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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants :	Carl-Axel Bauer *et al.*	Art Unit :	1617
Serial No. :	10/010,283	Examiner :	Jennifer M. Kim
Filed :	November 13, 2001	Conf. No. :	5064
Title :	NEW USE FOR BUDESONIDE AND FORMOTEROL		

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BRIEF ON APPEAL

Appellants are appealing the final rejection of claims 9, 11-17, and 21-58 in the Office Action dated June 15, 2006, and the Advisory Action dated December 4, 2006. A Notice of Appeal was filed and received by the U.S. Patent and Trademark Office on November 15, 2006.

(i) Real Party in Interest

The Real Party in Interest is AstraZeneca AB, the assignee of record, which is a subsidiary of AstraZeneca PLC.

(ii) Related Appeals and Interferences

There are no prior or pending related appeals, judicial proceedings, or interferences known to Appellants.

(iii) Status of Claims

Claims 1-8, 10, and 18-20 are canceled.

Claims 9, 11-17, and 21-58 are rejected and under appeal.

(iv) Status of Amendments

All previously filed amendments have been entered. No amendments are being submitted herewith.

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(v) Summary of Claimed Subject Matter

The claims are directed to methods of treating chronic obstructive pulmonary disease (COPD). Claims 9, 41, 52, 56, 57 and 58 are the independent claims.

Independent claim 9 is directed to a method for reducing the frequency and/or intensity of COPD exacerbations experienced by a patient suffering from COPD. The method includes administering to the patient via inhalation (i) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a second active ingredient which is budesonide, wherein the method is effective to reduce the frequency and/or intensity of exacerbations in the patient, the first and second active ingredients are administered simultaneously, and the molar ratio of (a) formoterol in the first active ingredient to (b) the second active ingredient is from 1:555 to 2:1. Support for independent claim 9 can be found, *e.g.*, at page 2, lines 1-25; and page 3, lines 12-16 and 30-31.

Independent claim 41 is directed to a method for the treatment of a patient suffering from COPD including administering to the patient via inhalation (i) a daily dose of a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and (ii) a daily dose of a second active ingredient that is budesonide. The daily dose of the first active ingredient delivers 2 to 120 nmol of formoterol to the patient, and the daily dose of the second active ingredient delivers 45 to 2200 μg of budesonide to the patient. The first active ingredient, which may be separate from or in admixture with the second active ingredient, is administered simultaneously with the second active ingredient, and the daily dose of each active ingredient is administered in one to four divided doses per day. Support for independent claim 41 can be found, *e.g.*, at page 3, lines 12-16; page 4, lines 4-7 and 23-25; and page 5, lines 1-4.

Independent claim 52 is directed to a method for treating a patient suffering from COPD including administering to the patient, via inhalation from a pMDI (pressurized metered dose inhaler), a composition comprising (i) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; (ii) a second active ingredient that is budesonide; and (iii) propellant P227. The molar ratio of (a) formoterol in the first active ingredient to (b) the second active ingredient is from 1:70 to 1:4. Support for

independent claim 52 can be found, *e.g.*, at page 2, lines 17-25; page 3, lines 12-15; page 4, lines 1-2; and page 6, lines 1-5 and 11-12.

Independent claim 56 is directed to a method for the treatment of a patient suffering from COPD including administering formoterol fumarate dihydrate and budesonide to the patient via inhalation. The formoterol fumarate dihydrate and budesonide are administered simultaneously and optionally in admixture; the amount of formoterol fumarate dihydrate inhaled by the patient is 18 μg per day; and the amount of budesonide inhaled by the patient is 640 μg per day. Support for independent claim 56 can be found, *e.g.*, at page 2, lines 17-25; page 3, lines 12-15; and page 5, lines 4-7.

Independent claim 57 is directed to a method for the treatment of a patient suffering from COPD including administering to the patient via inhalation (i) a daily dose of a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and (ii) a daily dose of a second active ingredient that is budesonide. The daily dose of the first active ingredient delivers an amount of formoterol to the patient per day that is equivalent to the amount delivered when 18 μg of formoterol fumarate dihydrate per day is delivered to the patient. The daily dose of the second active ingredient delivers 640 μg of budesonide to the patient per day. The first active ingredient is optionally in admixture with the second active ingredient, and the two active ingredients are administered simultaneously. Support for independent claim 57 can be found, *e.g.*, at page 2, lines 17-25; page 3, lines 12-15; and page 5, lines 4-7.

Independent claim 58 is directed to a method for the treatment of a patient suffering from COPD including administering formoterol fumarate dihydrate and budesonide to the patient via inhalation. The formoterol fumarate dihydrate and budesonide are administered simultaneously, and optionally in admixture, in one to four unit doses per day; the amount of formoterol fumarate dihydrate delivered to the patient by each unit dose of formoterol fumarate dihydrate is 4.5 μg; and the amount of budesonide delivered to the patient by each unit dose of budesonide is 160 μg. Support for independent claim 58 can be found, *e.g.*, at page 2, lines 17-25; page 3, lines 12-15; and page 4, lines 23-25.

(vi) Grounds of Rejection to be Reviewed on Appeal

Whether claims 9, 11-17, and 21-58 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Carling *et al.* (WO 93/11773) in view of Cazzola *et al.* ("Effect of Salmeterol and Formoterol in Patients with Chronic Obstructive Pulmonary Disease" *Pulmonary Pharmacology* 7:103-107, 1994) and Renkema *et al.* ("Effects of Long-term Treatment with Corticosteroids in COPD" *Chest* 109:1156-1162, 1996) and further in view of Giardina *et al.* (U.S. Patent No. 6,227,862 B1).

(vii) Argument

Rejection under 35 U.S.C. § 103(a) over Carling *et al.* in view of Cazzola *et al.* and Renkema *et al.* and further in view of Giardina *et al.*

The present claims are drawn to methods of treating chronic pulmonary obstructive disease (COPD). Prior to addressing the grounds for rejection, Appellants believe it may be useful to explain some of the characteristics of this disease. COPD is a chronic and progressive disease of the airways typically seen in long-term cigarette smokers. It involves both emphysema (a lung condition in which the air sacs are permanently damaged, leading to loss of lung surface and elasticity, thereby impairing the gas exchange capacity of the lungs and the patient's ability to exhale) and chronic bronchitis (a persistent inflammation of the air passages characterized by excessive production of mucus). COPD patients exhibit chronic symptoms such as cough, shortness of breath ("dyspnea"), chest tightening, excessive sputum, wheezing, and impaired physical capacity. A common measure of the severity of the disease is the patient's "forced expiratory volume in one second," or FEV1, often expressed in comparison with the FEV1 that would be predicted for a healthy person of the same age and size. FEV1 is determined by measuring the volume of air that the patient can forcibly exhale in one second. A COPD patient having FEV1 ≥ 80% of predicted FEV1 is categorized as having mild COPD, while a patient having 50 % ≤ FEV1< 80 % of predicted FEV1 is categorized as having moderate COPD, and a patient having 30 % ≤ FEV1 < 50 % of predicted FEV1 is categorized as having severe COPD. A patient whose FEV1 is < 30 % predicted, or <50% predicted and accompanied by chronic respiratory failure, is categorized as having very severe COPD. See,

e.g., page 7, Figures 1-2, of "GOLD: Global Initiative for Chronic Obstructive Lung disease; Global Strategy for the Diagnosis, Management, and prevention of Chronic Obstructive Pulmonary Disease," based on April 1998 NHLBI/WHO Workshop, pages 1-100 (2004 update); page 7 is included as Item 1 in the Evidence Appendix. This chronic impairment in lung function worsens over time, and can be increasingly debilitating, leaving the patient less and less able to carry out a normal daily routine. In addition, the more severely affected patients occasionally experience acute exacerbations of their COPD symptoms in which their clinical status deteriorates markedly over a short time (typically 10-15 days), to the point that they become bedridden or even require hospitalization. Repeated exacerbations will accelerate the decline in lung function and health status. These crisis episodes cause extreme distress to the patient (the exacerbation episodes have been likened to a feeling of "drowning"), and can be fatal. In fact, COPD is currently ranked as the fourth most common cause of death throughout the world.

Appellants have unexpectedly found that treating a COPD patient with a combination of <u>formoterol (or a salt or solvate thereof, or a solvate of such a salt) plus budesonide</u> can reduce the frequency and/or intensity of exacerbations, as well as improve the patient's lung function (measured by FEV1) more effectively than either of the agents alone. This represents a dramatic step forward in the treatment of this difficult disease.

The pending claims are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* in view of Cazzola *et al.* and Renkema *et al.* and further in view of Giardina *et al.*

Analysis and determination of obviousness under § 103(a) requires determination of the scope and content of the prior art, differences between the prior art and the claims in issue, and the level of ordinary skill in the pertinent art. <u>Graham v. John Deere</u>, 383 U.S. 1, 17 (1966). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must by some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. Second, there must be a reasonable expectation of success, and third, the prior art references when combined must teach or suggest all the claim limitations. MPEP 2143. Furthermore, when applying

§ 103(a), the following tenets of patent law must be adhered to: (A) the claimed invention must be considered as a whole; (B) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) a reasonable expectation of success is the standard with which obviousness is determined. MPEP 2141(II), citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). Also, objective evidence of considerations such as unexpected results and skepticism of experts is relevant to the issue of obviousness and must be considered in every case in which it is present. When evidence of any of these considerations is submitted, the examiner must evaluate the evidence. MPEP 2141 (III). The ultimate determination on patentability is made on the entire record. MPEP 2141 (III), citing *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The Examiner summarized her basis for the rejection of the claims under 35 U.S.C. § 103(a) in the Final Office Action dated June 15, 2006 (hereinafter "the June 15, 2006, Office Action"). In the June 15, 2006, Office Action, at page 4, the Examiner stated that Carling *et al.* "teach a medicament containing effective amounts of formoterol and budesonide in combination for simultaneous, sequential or separate administration by inhalation in treatment of respiratory disorder..." The Examiner, however, conceded that Carling *et al.* does not expressly teach the treatment of COPD. June 15, 2006, Office Action at page 5. According to the Examiner, Cazzola *et al.* teaches that formoterol is effective in patients with COPD; Renkema teaches that treatment with corticosteroids (*i.e.*, budesonide) significantly reduced pulmonary symptoms in patients with COPD; and Giardina *et al.* reports that COPD and asthma are respiratory disorders. Id. The Examiner concluded that it would have been obvious to use Carling's medicament in

> reducing the frequency and/or intensity of COPD since COPD is a well-known respiratory disease as disclosed by Giardina et al., and Giardina et al. teach that the combination is useful for the treatment of respiratory disorders[1]...One of ordinary skill in the art would have been motivated to employ Carling's medicament in reducing the severity or intensity or

[1] The statement that "Giardina et al teach that the combination is useful for the treatment of respiratory disorders" is plainly not true, as Giardina *et al.* teach nothing at all about the presently claimed combination. Since nowhere else does the Examiner make such an assertion about Giardina *et al.*, Appellants assume that the Examiner meant to refer here to Carling instead of Giardina *et al.* Appellants' arguments are based on that assumption.

> frequency of having COPD with reasonable expectation of success since each of the active agents utilized in Carling's medicament are well known individually for effectively treating...COPD. Absent any evidence to the contrary, there would have been a reasonable expectation of successfully treating COPD by employing Carling's formulation...
> June 15, 2006, Office Action at pages 5-6.

Appellants disagree with the Examiner's characterization of the prior art. As elaborated below, Appellants maintain that Carling *et al.* teaches a combination of budesonide and formoterol *solely for the treatment of asthma and disorders like asthma, i.e.*, disorders that are bronchospastic in nature. The teachings of the prior art provide no guidance that would lead one of ordinary skill in the art to expect that a combination therapy of budesonide and formoterol could be used to treat COPD with any reasonable expectation of success, and in fact *teach away* from such a therapy.

Appellants traverse the rejection on a number of grounds, including the following:

1. The references do not provide either the motivation or the expectation of success necessary to make a *prima facie* case of obviousness;
2. The prior art as a whole actually teaches away from the claimed methods;
3. The surprising results observed by Appellants are cogent, objective evidence that the claimed methods cannot be deemed obvious; and
4. Even years after the present application's priority filing date (September 19, 1997), experts in the field of respiratory therapy continued to express doubt that budesonide (whether alone or in the claimed combination therapy) would be useful for treating COPD.

Each of these points is addressed in turn below. Appellants begin by presenting arguments that apply to all of the pending claims, and then discuss further arguments that apply to particular sub-groupings of claims.

1. No motivation nor expectation of success

The primary reference is Carling, cited for its disclosure of use of a budesonide/ formoterol combination for treatment of what Carling describes as "respiratory disorders such as asthma." Carling at page 1, lines 12-13. The Examiner acknowledges that Carling did not mention treatment of COPD in particular, but argues that, because COPD is known to be a

respiratory disorder (citing Giardina *et al.*), one of ordinary skill would have interpreted Carling's mention of "respiratory disorders" to encompass COPD. See, *e.g.*, the Office Action dated May 4, 2005, at page 6 ("the May 4, 2005, Office Action"). Since there is no more reason to read Carling's term as encompassing COPD than as encompassing any other randomly selected respiratory disorder, the Office action is essentially saying that Carling teaches use of the budesonide/ formoterol composition for treatment of <u>all</u> conditions that have ever been classified by anyone as "respiratory disorders." This cannot be a reasonable interpretation of Carling. In view of the wide variety of unrelated conditions that can be classified as respiratory disorders (including, for example, such varied conditions as cough, pulmonary vascular hypertension [a condition that affects pulmonary blood vessels, not the airways], lung cancer, cystic fibrosis and tuberculosis), reading Carling as teaching that one mode of treatment will work for <u>all</u> respiratory disorders is contrary to common sense. Appellants have presented a multitude of evidence that those of skill in the art understand asthma and COPD to be fundamentally different diseases, with different causes and different treatments. For example, the editorial by K.F. Rabe (*Eur. Respir. J.* <u>22</u>:874-875, 2003; Item 2 in the Evidence Appendix) shows that, *even in 2003, long after the present application's priority date (September 19, 1997),* an expert in the field of respiratory disease repeatedly asserted that COPD and asthma are fundamentally different diseases that are unlikely to be successfully treated the same way. At page 874, left column, the author noted:

> We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically....[Were] we all wrong, does this mean we no longer need to differentiate between asthma and COPD since the treatment will be the same in the end?

Dr. Rabe later emphasizes that "these two diseases...are <u>fundamentally different</u> in the vast majority of patients." Rabe at page 875, left column (emphasis added).

In the June 15, 2006, Office Action, the Examiner cited, *inter alia*, the 16th Edition Merck Manual (1992) ("the 1992 Merck Manual"; Item 3 in the Evidence Appendix) for its teaching of the interrelationship between COPD and asthma. Appellants believe the Examiner has misinterpreted the teachings of the 1992 Merck Manual, as it actually <u>distinguishes</u> between asthma and COPD by pointing out that the two conditions are quite different and are treated in

different ways. For example, at page 659, the 1992 Merck Manual states that **"most asthmatics...have a disease that is almost totally reversible and should not be confused with COPD."** Also at page 659, the 1992 Merck Manual states that **"whenever possible, persons with chronic asthmatic bronchitis should be distinguished from those with a primarily emphysematous type of COPD since the course, prognosis, and response to therapy are distinctly different."** "Asthma" *per se* (as opposed to "chronic asthmatic bronchitis") is addressed under its own heading in a different part of the 1992 Merck Manual (at pages 646-657), so is even more clearly differentiated from COPD.

Other teachings in the art before the 1997 priority date of the application also distinguish between asthma and COPD. Renkema (1996), for example, states at page 1156, column 1: **"The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. In contrast, their effectiveness in patients with COPD is controversial, especially during a stable phase of the disease."** Renkema also recognizes that it is important for their study to distinguish COPD patients from asthma patients, stating **"to assess the effectiveness of these drugs in patients with COPD, it is...essential to exclude patients with asthma."** Renkema at page 1160, column 2. Renkema explains, **"There is general agreement that the inflammatory processes involved in the pathogenesis of the two disease entities are different in nature, and it is not inconceivable that the inflammatory processes in COPD are less sensitive to the anti-inflammatory action of corticosteroids."** Id. at page 1161, column 2. There is no question that at the filing date of the application, asthma and COPD were recognized as distinct disorders with different causes and different treatments.

In view of the above, Appellants maintain that Carling's use of the term "respiratory disorders" should be read in the context in which one of ordinary skill in the art in 1997 would have read it: *i.e.*, to encompass disorders that are bronchospastic in nature, similar to asthma. It does not make any sense to read the term so as to sweep in all respiratory diseases, even those quite different from asthma. A Declaration by Jan Trofast, submitted March 1, 2004, (hereinafter, the "2004 Trofast Declaration"; Item 4 in the Evidence Appendix) also includes statements to this effect. In the May 4, 2005, Office Action, responding to these arguments and the statements in the Declaration, the Examiner merely reiterated that, because Giardina *et al.* (a reference with no relevance to the presently claimed invention) classified COPD as a

"respiratory disorder," the 2004 Trofast Declaration was "not persuasive." Appellants maintain that one must interpret the language of the Carling reference in a way that is internally consistent, and not distort it beyond what Carling could possibly have meant, simply to serve the purpose of making out the elements of an obviousness rejection. The 2004 Trofast Declaration makes it clear that, in the context of the Carling reference, the term "respiratory disorders such as asthma" means not ALL respiratory disorders, but rather those respiratory disorders similar to asthma, *i.e.*, mainly of bronchospastic nature. This would not include COPD. This is entirely consistent with the other evidence of record. The Examiner has offered no reason to justify an interpretation broader than Appellants', other than the fact that a broader interpretation can be found in an unrelated reference on a completely different topic. Since all of the claims are limited to treatment of COPD, none can be said to be obvious in view of Carling's mention of "respiratory disorders."

In further support of the rejection, the Examiner argues that Cazzola *et al.* teaches that formoterol alone "is effective in patients with COPD" and that Renkema teaches that budesonide alone "significantly reduced pulmonary symptoms in COPD patients." Appellants maintain that the prior art, when taken as a whole, provided neither motivation nor expectation of success regarding use of budesonide for treatment of COPD. Appellants' arguments in support of this position are developed in the following section 2, which discusses how the art, when taken as a whole, actually *teaches away* from the presently claimed methods. If the art teaches away from a particular method, clearly it can provide to the skilled reader neither motivation to try nor expectation of success if one were to try.

2. Teaching away

That the art, taken as a whole, actually *taught away* from any use of budesonide (alone or in combination with another drug) to treat COPD can be seen from a careful consideration of what the art of record actually teaches. First, the evidence available at the present application's priority date established that short-term use of budesonide alone (at any dosage) would not provide any benefit in the treatment of COPD. Renkema himself notes this in the first paragraph on page 1156. **Thus, the art teaches away from such short-term use of budesonide, regardless of the dose.** Second, Renkema's long-term trials of budesonide treatment, which

employed a relatively high dose of 1600 µg budesonide per day, demonstrated what Renkema characterized as "limited" beneficial effects in COPD patients. Renkema at page 1161, column 2, last paragraph. Renkema's modest results rule out any reason to attempt trials with lower doses of budesonide; indeed, Renkema himself states, **"It may be that still higher doses of corticosteroids are needed in patients with COPD."** Id. at page 1161, column 2, second paragraph. This can be taken as a teaching-away from use of anything less than 1600 µg budesonide per day. Since Renkema teaches away from using lower doses at all, and teaches away from short term use of budesonide at any dose, this leaves only the question of whether it would have been obvious to try using high doses of at least 1600 µg budesonide (combined with formoterol) for long term treatment.

In view of other art of record, this plainly would not be the case.

Smeenk *et al., Nederlands Tijdschrift voor Geneeskunde* 140:94-98, 1996 ("Smeenk"; Item 5 in the Evidence Appendix) suggests that the long-term use of a daily dose of 1600 µg budesonide is not associated with a positive benefit/risk ratio. This reference reports that 800-1600 µg budesonide per day is associated with an unexpectedly high rate of opportunistic lung infections in COPD patients. According to the authors,

> Inhalation corticosteroids are of great importance in the treatment of asthmatic patients. Their place in the treatment of patients with COPD is much less clear....The high dosages of inhalation corticosteroids may have been involved in the cause of these infections by suppressing the T-cell response locally. In view of this, longterm inhalation corticosteroid treatment should be prescribed in COPD patients only if the efficacy of the medication has been proved in the individual patient involved.

This teaching that inhaled corticosteroids (particularly in doses above 800 µg per day) are of uncertain benefit in COPD patients and are associated with an unexpectedly high rate of opportunistic lung infections, and that long term inhaled corticosteroid treatment should be prescribed only in limited situations, **is plainly a teaching-away from long term treatment of COPD patients with high doses of corticosteroids in general, and budesonide in particular.** This teaching-away tempers any reading of Renkema that would suggest high-dose budesonide (*i.e.*, over 1600 µg per day) has possible benefits in COPD. One of ordinary skill in the art, reading both Renkema and Smeenk, would come away with the understanding that (1) if

budesonide has any role in treatment of COPD, it would be only if it were used in <u>large doses</u> (at least 1600 μg per day) over a <u>long term</u>, but (2) unfortunately such use would carry a risk of pulmonary infection due to immunosuppression that in most cases would outweigh any benefit to the patient. There is certainly no incentive derivable from these references to investigate use in COPD patients of a <u>combination</u> treatment involving budesonide and a second active ingredient, particularly since such a combination treatment would make it unclear what benefits (if any) the patient might be deriving from the budesonide part of the combination to counterbalance the very real risks of taking large doses of corticosteroids long term. **In sum, the art teaches away from use of budesonide (either alone or in combination with a second active ingredient) for the short- or long-term treatment of COPD, whether at <u>low</u> doses (which Renkema suggests won't be of any value) or <u>high</u> (which Smeenk teaches increase the risk of infections while providing no clear benefit), leaving no dose of budesonide that the art would consider adequately effective to justify the risk.** Accordingly, **<u>all</u>** of the claims—even those that do not specify a particular dose of budesonide—are nonobvious in view of the art, taken as a whole.

<u>3. Surprising results</u>

As still another basis for withdrawal of the rejection of the claims, Appellants note the extensive evidence of surprising results of record in this case, evidence that the Examiner continues to dismiss for reasons that are presently unclear, but at one point were stated as being because "Applicants' claims are not drawn to alleged synergism." May 4, 2005, Office Action at page 7. If that remains at least part of the rationale, Appellants note that U.S. law does not require that claims be "drawn to synergism" in order for surprising results to be taken as conclusive evidence of nonobviousness. See, for example, <u>Knoll Pharmaceutical Company, Inc. v. Teva Pharmaceuticals USA, Inc.</u>, 367 F.3d 1381 (Fed. Cir. 2004) and <u>In re Chu</u>, 66 F.3d 292 (Fed. Cir. 1995), where the court held that evidence of surprising results must be considered and can be dispositive of nonobviousness even if the evidence is not disclosed in the specification as filed. (If the evidence need not be in the specification as filed, it certainly need not be recited in the claims.)

The Examiner's rationale for dismissing Appellants' evidence of unexpected results was stated somewhat differently on page 8 of the June 15, 2006, Office Action:

> With regard to argument 3), it is not persuasive because Applicants' data has been carefully reviewed and considered. However, the prior art Carlings et al. teach that the combination of formoterol and budesonide gives greater efficiency in treatment of respiratory disorders. (page 4, lines 3-10). Therefore, the teaching encompasses Applicant's data of having synergistic effect of either agent employed alone. Carlings et al. teach same combination having same ratio for the greater efficiency of treating respiratory disorder which includes COPD. Therefore, the greater efficiency result of treating COPD is expected and taught by Carlings. (*Nonstandard English and misspellings in the original.*)

The portion of Carling cited in this passage actually says nothing about COPD; indeed, Carling never mentions this disorder, which (as Appellants established above) is quite different from the sort of respiratory disorder one of ordinary skill in the art would have considered to be treatable in a manner similar to the condition that *is* taught by Carling: asthma. Furthermore, if the Examiner truly believes that the many, varied, and completely unexpected synergistic results submitted by Appellants in support of this application can be summed up as nothing more than the "greater efficiency" mentioned by Carling, she is urged to again review Appellants' data. Such evidence was submitted, *e.g.*, in a declaration by Jan Trofast submitted April 25, 2002 ("the 2002 Trofast Declaration"; Item 6 in the Evidence Appendix) and a declaration by Christer Hultquist submitted December 13, 2002 (Item 7 in the Evidence Appendix), each describing the results of clinical trials demonstrating unexpectedly better results with the presently claimed combination treatment, compared to treatment of COPD with either budesonide or formoterol alone. Another declaration of Jan Trofast (the "2005 Trofast Declaration"; Item 8 in the Evidence Appendix) was submitted November 4, 2005.

Below, Appellants briefly summarize the data presented with the 2005 Trofast Declaration. The declaration itself and Calverley *et al.* (*Eur. Resp. J.* 22:912-919, 2003; Item 9 in the Evidence Appendix) provide a fuller description of the data than is given here, and should be read in conjunction with this summary.

The graphs submitted as Appendices 1-9 with the 2005 Trofast Declaration (and attached to that Declaration in the Evidence Appendix) illustrate data collected from a placebo-controlled

12-month clinical trial that was performed using a combination of budesonide/formoterol fumarate dihydrate (under the product name Symbicort®) in the treatment of moderate to severe COPD. (Formoterol is the biologically active moiety in formoterol fumarate dihydrate (FFD).) Before randomization, 1022 patients were treated in a 2 week initial run-in period with oral prednisolone (30 mg once daily), inhaled FFD (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose[2] of 6.0 μg FFD), and terbutaline as needed (Bricanyl®; 0.5 mg by inhalation). The patients had the following profile:

Age $\geq$ 40 years
COPD diagnosis since at least 2 years prior to the study
At least 10 pack years smoking history[3]
Documented use of inhaled bronchodilators as a quick relief medicine
At least one severe COPD exacerbation within 2-12 months of entry
$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator
$FEV_1/VC \leq 70\%$ pre-bronchodilator
(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

All of the following medications and the placebo were delivered from a Turbuhaler® inhaler. The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/FFD combination (Symbicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide/4.5 μg FFD to the patient (corresponding to a metered dose of 200 μg budesonide and 6.0 μg FFD for the monoproducts))

Group 2: Budesonide alone (Pulmicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide to the patient from a metered dose of 200 μg budesonide)

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[2] A "metered dose" is the amount of product that is positioned in the inhaler for delivery to the patient with each puff. Not all of the metered dose is delivered to the patient; some product will stick to the sides of the inhaler, or will otherwise remain in the inhaler. A "delivered dose" is the amount of product that exits the inhaler. This amount is less than the metered dose.

[3] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

Group 3: FFD alone (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose of 6.0 μg FFD)

Group 4: Inhaled placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded. The results of this study suggest that the combination of budesonide and FFD (*i.e.,* formoterol) produces quite pronounced synergistic effects by several different measures.

First, as shown in the graph titled "Symbicort reduces the risk of first exacerbation requiring medical intervention"[4] (Appendix 1 attached to the 2005 Trofast Declaration), the hazard rate was reduced (compared to placebo) by **28.5 %** in patients treated with the budesonide/FFD combination. The corresponding reduction for patients treated with <u>budesonide alone</u> was **7.5 %,** while <u>FFD alone</u> actually produced an <u>increase</u> (compared to placebo) of **1.5 %**. A merely additive effect would have produced a 6.0 % reduction[5]. Thus, it is clear that the combination product produced a synergistic effect.

Second, the graph titled "Symbicort reduces the number of severe exacerbations/patient/year" (Appendix 2 attached to the 2005 Trofast Declaration) also strongly implies a synergistic effect of the budesonide/FFD combination therapy. As compared to treatment with placebo, treatment with FFD alone actually <u>increased</u> the number of exacerbations per patient per year slightly (**+3%**), while treatment with budesonide alone decreased the number of exacerbations per patient per year by **12%**. **Patients treated with the budesonide/FFD combination, however, exhibited a <u>24%</u> reduction in exacerbations.** This result demonstrates a synergistic effect, as the 24% reduction is much greater than the 9% reduction expected if the effect of the combination therapy were merely additive.

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[4] Severe exacerbations were considered to be exacerbations requiring medical intervention, *i.e.*, administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

[5] In order to assure the stability of the first order approximation used above to assess the additive effects, a fully elaborated approach is also presented. By treating these data in a multiplicative way (the model being relative), the additive effect of budesonide and formoterol is = 100 – (100-7.5)*(100+1.5)/100 = 6.1 % and the combination (Symbicort®) over this is = 100 - 100*100*(100-28.5)/((100-7.5)*(100+1.5)) = 23.8 %. Note that this effect is even greater than suggested above (= 28.5-6.0 = 22.5 %), showing that calculation on the additive scale gives a conservative estimate.

Third, a synergistic effect was also indicated in the patients' need for oral steroids during the course of the study, as shown in the graph titled "Symbicort reduces need for oral steroids" (Appendix 3 attached to the 2005 Trofast Declaration). Treatment with budesonide alone reduced the hazard rate of time to first oral steroid use by **14%** compared to placebo, and treatment with FFD alone reduced the hazard rate by **13%** as compared to placebo. **In contrast, treatment with the budesonide/FFD combination reduced the hazard rate of time to first oral steroid by <u>42.3%</u> versus placebo.** This is far better than the 27% reduction that would have been expected from an additive effect of the individual budesonide and FFD components.

Fourth, a synergistic effect was also observed in the effect on night awakenings, as shown in the graph titled "Symbicort increases nights without awakenings" (Appendix 4 attached to the 2005 Trofast Declaration). Treatment with either budesonide alone or FFD alone resulted in an adjusted mean change in awakenings-free nights of **+3.7 %** (compared to placebo). If budesonide and FFD in combination had a merely additive effect on the change in awakenings-free nights, the adjusted mean change of the combination therapy (compared to placebo) would be expected to be **+7.4 %.** However, treatment with the combination therapy resulted in an adjusted mean change in awakenings-free nights (compared to placebo) of **<u>+ 9.2 %,</u>** much greater than the calculated additive effect of 7.4 %.

Fifth, a synergistic effect was also indicated in the morning peak expiratory flow (PEF), as shown in the graph titled "Symbicort rapidly improves and maintains morning PEF" (Appendix 5 attached to the 2005 Trofast Declaration). The difference in adjusted mean change of morning PEF, as compared to placebo, was **3.5** L/min for the patients treated with budesonide alone, **11.1** L/min for those treated with FFD alone, **and 18.3 L/min for the patients treated with the budesonide/FFD combination,** *i.e.*, 3.7 L/min higher than would be expected if the effect were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002 (as noted above, Item 7 in the Evidence Appendix), and supplement the data presented in Calverley *et al.* at page 915, column 2 and in Figure 3(a) at page 916.

Sixth, the graph titled "Symbicort rapidly improves and maintains evening PEF" (Appendix 6 attached to the 2005 Trofast Declaration) strongly implies a synergistic effect on the patients' evening peak expiratory volume (PEF). The difference in adjusted mean change of

evening PEF, as compared to the placebo, was **2.0** L/min for the patients treated with budesonide alone, **8.9** L/min for those treated with FFD alone, and **14.1 L/min for the patients treated with the budesonide/FFD combination**, *i.e.*, 3.2 L/min higher than would be expected if the effect of the budesonide/FFD combination were merely additive.

Seventh, the graph titled "Symbicort produces rapid and maintained improvement in lung function (FEV1)" (Appendix 7 attached to the 2005 Trofast Declaration) illustrates that FEV1 decline was less severe in patients treated with a budesonide/FFD combination therapy than in those treated with either monotherapy. The combination therapy was **14%** better than placebo in this regard while the monotherapies were only **8%** and **2%** better than placebo. Also, as illustrated by the graph titled "Symbicort improves health related quality of life, HRQL" (Appendix 8 attached to the 2005 Trofast Declaration), the mean change in total score on St. George's Respiratory Questionnaire (SGRQ) as compared to placebo was **-7.5**, which was a greater improvement than that observed following treatment with budesonide alone (**-3.0**) or FFD alone (**-4.1**)[6].

Finally, as illustrated by the graph titled "Symbicort reduces discontinuations compared to other treatments" (Appendix 9 attached to the 2005 Trofast Declaration), fewer patients withdrew from the study when they received the budesonide/FFD combination therapy than when they received either of the monotherapies. These data supplement the data in Table 1 of Calverley *et al.* at page 914, which reports that **71%** of the patients originally enrolled in the study and who received treatment with the combination of budesonide and FFD completed the study. By comparison, only **59%** of patients receiving placebo completed the study, approximately the same as those receiving FFD alone (**56%**) or budesonide alone (**60%**). The multiple beneficial effects described above may have contributed to the fact that fewer patients receiving the budesonide/FFD combination therapy withdrew from the study.

Appellants submit that the above clinical evidence is proof, many times over, that the presently claimed methods produce results that could not have been predicted from anything in the art. Each of these separate observations of synergistic effects was unexpected and thus important evidence of nonobviousness. Under U.S. law, any objective indicia of

[6] A change of *minus* 4 points in the SGRQ represents a clinically important improvement in health related quality of life. The more negative the score, the better the quality of life.

non-obviousness, such as surprising results, must be taken into account when considering whether the claims are obvious over prior art. Though the Examiner claims to have duly considered the data, the fact that she found it "unpersuasive" merely because Carling mentions that the same combination of drugs, *when used to treat asthma*, has "greater efficiency" than the single drugs alone suggests that she did not seriously take the data into account. Carling provides no indication that one could expect the dramatic effects of record in the present case in relation to COPD. The Examiner simply makes the leap that the "synergism" that she reads into Carling applies not only to treatment of asthma, *but also to treatment of every other condition Giardina et al. (an unrelated reference that the Examiner has apparently randomly selected even though it deals with unrelated subject matter) happens to characterize as a "respiratory disorder*." This leap is not justified by the facts.

The court in In re Soni, 54 F.3d 746, 751 (Fed. Cir. 1995), stated that "when an applicant demonstrates *substantially* improved results...and *states* that the results were unexpected, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." (Emphasis in original). Appellants have presented such results and stated that they were unexpected. (See, *e.g.*, the March 1, 2004, Trofast Declaration, Item 4 in the Evidence Appendix, in which Dr. Trofast described the results presented in Calverley *et al.* showing the effect of the combination of formoterol and budesonide to reduce the frequency of COPD exacerbations as **"surprising given the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone."** March 1, 2004, Trofast Declaration at page 5.) The Examiner has failed to provide any legitimate "evidence to the contrary," as required by In re Soni. Therefore, Appellants' evidence of unexpected results described in the Trofast declarations and the Hultquist declaration of record must be given due weight as cogent and persuasive evidence of nonobviousness.

4. Skepticism of Experts

As a final, independent ground for establishing the nonobviousness of the claimed methods, Appellants note the substantial evidence of record concerning skepticism of experts, one of the standard objective indicia of nonobviousness recognized under U.S. law (see, *e.g.*, Graham v. John Deere, 383 U.S. 1 (1966)). For example, the above-cited editorial by K.F. Rabe

shows that though this expert was "happy to adopt" use of formoterol/budesonide combination therapy for treatment of asthma, **he was skeptical that the combination could be generally useful in treatment of COPD.** That the author could still be skeptical in 2003, following publication of two clinical trials disclosing the benefits of the combination therapy in COPD, suggests how entrenched the assumption was that these drugs (or at least budesonide) would have no value in treating COPD. Another post-filing date article (Vestbo et *al., Lancet* 353:1819-1823, 1999; Item 10 in the Evidence Appendix) flatly states in the abstract, **"Inhaled budesonide was of no clinical benefit in COPD patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD."** It is clear from such post-filing date evidence that the art was skeptical that budesonide alone or in the claimed combination therapy was of any value in treating COPD, even years after Appellants' priority date. The Examiner has not explained why something about which the experts in the art were clearly skeptical would have been "obvious" to everyone else.

In summary, Appellants have established

1. that the cited art provided neither motivation to carry out the claimed methods, nor expectation of success upon doing so;
2. that the art actually taught away from the claimed methods;
3. that administration of the claimed combination produces unexpected and synergistic results; and
4. that the bias in the art against the usefulness of inhaled corticosteroids in treating COPD was so pronounced that it remained even years after Appellants' filing date.

Any one of these points would be sufficient to mandate withdrawal of the rejection. Taken together, the weight of the evidence is overwhelming.

In addition to the above arguments and evidence, which apply to all of the claims, Appellants note that various independent and dependent claims include limitations that provide further grounds for distinguishing the art. These claims are discussed in three groupings below

(groupings I, IIA, and IIB). A few claims contain limitations appropriate to two of these groupings, so are discussed in both.

I. Claims 9, 11-17, 21-40, 50 and 54

Each of these claims recites that the method "is effective to reduce the frequency and/or intensity of [COPD] exacerbations in the patient" (claim 9 and its dependents) or "produces a reduction in frequency or intensity of COPD exacerbations in the patient" (claims 50 and 54). These limitations are neither taught nor even suggested by any of the prior art. Renkema reported that, while certain subjective "symptom scores"[7] did decrease during long-term treatment with budesonide alone, neither airflow obstruction (as measured by FEV1) ***nor the frequency or duration of exacerbations*** was affected by treatment with budesonide. Renkema at page 1160 at column 1. None of the other cited references even mentions COPD **exacerbations.** Cazzola *et al.* focused solely on airflow obstruction (measuring FEV1), not exacerbations, in their formoterol study subjects. Carling, as discussed above, was concerned solely with asthma and asthma-like disorders, so had no reason to look at COPD exacerbations, and indeed did not. Giardina is simply irrelevant. Given that there was no reason to expect that either budesonide alone or formoterol alone would be effective in reducing the frequency or intensity of COPD **exacerbations**, and in fact Renkema affirmatively teaches that budesonide alone is not effective for that purpose, one of ordinary skill would not have been motivated to try them in combination for this purpose, as required by pending claims 9, 11-17, 21-40, 50 and 54—and certainly would not have had any reasonable expectation of success even if the experiment had been attempted.

Rather than being convinced by this evidence, the Examiner apparently believes that Renkema's negative results regarding effectiveness against exacerbations should be read as positive ones. According to Renkema, **"No significant changes in exacerbation frequency or duration during the study were observed"** in any of the test subjects. Renkema at page 1160,

[7] The symptom score is described at the top of the second column on page 1157: "Patients were asked to rate the severity of dyspnea (scale, 0 to 5), dyspnea on exertion (scale, 0 to 3), early morning dyspnea (scale, 0 to 3), cough (scale, 0 to 3) and wheeze (scale, 0 to 3). A score of 0 was given if the complaint was absent; a higher value corresponded with increasing severity. A total complaint score (scale, 0 to 17) was calculated by adding up the scores from each question." Dyspnea is difficult or labored breathing. The "symptom score" is thus derived from the patient's own subjective characterization of his difficulty in breathing, rather than on an objectively quantifiable measure such as FEV1 or number of hospitalizations for exacerbations.

column 1. The Examiner dismissed the significance of this observation by Renkema, stating at page 8 of the June 15, 2006, Office Action that Renkema's finding of no treatment effect on frequency or duration of exacerbations was "due to high number of withdrawals only."

This is not what Renkema says.

Renkema actually states only that the observed lack of efficacy **"may have been biased by the pattern of withdrawal."** Renkema at page 1161, column 1. Renkema's speculation as to a possible problem with the data cannot be taken to be a teaching that the frequency and/or intensity of COPD exacerbations can be reduced by treating a COPD patient with budesonide, either alone or in combination with formoterol. Negative results are negative results, and are not turned into positive results just because the author of the study points out possible weaknesses in the data. Cazzola also does not teach that formoterol alone can reduce exacerbations in patients with COPD, and Carling does not mention COPD, much less COPD exacerbations. Thus, none of the cited references teaches that either formoterol or budesonide, alone or in combination, can be expected to have any effect on exacerbations in patients with COPD, and in fact Renkema reports that *no benefit* in this regard was observed with budesonide, thereby *teaching away* from further attempts to reduce COPD exacerbations using budesonide-containing compositions. This is an additional reason that claims 9, 11-17, 21-40, 50, and 54 in particular are patentably nonobvious over the cited references.

IIA. Claims 28, 34, 36, 43, and 56-58

IIB. Claims 38, 40, 46 and 53

All of the listed claims (claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58) require particular daily doses or daily dose ranges of budesonide that are far less than 1600 μg/day, the only level tested by Renkema. They are grouped into two sub-groups because the maximum daily dose specified in the claims of grouping IIA is different from that specified in grouping IIB, so their patentability over the cited art should be considered separately.

The claims of group IIA all specify a daily dose that is **640 μg/day** or less. Claims 28 and 34 state that the 160 μg unit doses of budesonide specified in claims 27 and 33, respectively, are administered one to four times per day; this would result in a daily dosage of **160 to 640 μg**. Claim 58 similarly requires delivery of **160 to 640 μg/day** (one to four unit doses of 160 μg

each). Claims 36 and 43 specify that the amount is **320 to 640 μg/day** (1 or 2 unit doses at 320 μg per unit dose). Claims 56 and 57 are simply limited to a dose of **640 μg/day**.

The maximum daily dosage of budesonide permitted in the claims of grouping II.B. (claims 38, 40, 46 and 53) is even lower: **320 μg/day**. Claim 38 requires that the 80 μg unit dose of claim 37 be administered one to four times per day, resulting in a daily dosage of **80 to 320 μg/day.** Claims 40 and 46 are both limited to administration of a 160 μg unit dose once or twice per day, for a total of **160 to 320 μg/day.** The daily dose specified in claim 53 can range from **80 to 320 μg/day.**

The Examiner cited no art that would indicate any of these budesonide daily doses or dosage ranges would have any value in treating COPD. Renkema taught that even a much <u>higher</u> dose of budesonide (1600 μg per day) provided only modest benefit and proposed that still higher doses should be tested, thereby profoundly teaching away from the far lower daily dose/dosage ranges required by the claim in groupings II.A. and (even more so) IIB. As discussed above, Renkema's long-term trials of budesonide treatment at 1600 μg per day resulted in what Renkema characterized as "limited" beneficial effect in COPD patients. Renkema at page 1161, column 2, last paragraph. Renkema's modest results rule out any reason to attempt trials with lower doses of budesonide. Indeed, Renkema himself states, **"It may be that still higher doses of corticosteroids are needed in patients with COPD."** Renkema at page 1161, column 2, second paragraph. This can be taken as a teaching-away from use of anything less than 1600 μg budesonide per day for treatment of COPD, and certainly means that one of ordinary skill would find neither motivation nor expectation of success upon employing doses of budesonide below 1600 ug per day. As discussed above, the post-filing date clinical trial of budesonide reported by Vestbo *et al.* (Item 10 in the Evidence Appendix) demonstrated that a daily dose of **1200 μg** for six months followed by **800 μg** daily for 30 months produced no clinical benefit in COPD patients, entirely consistent with the teaching-away of Renkema. Yet the Examiner inexplicitly ignores this evidence and persists in saying that the claimed methods are "obvious."

Appellants submit that the claims of groupings IIA and IIB are patentable on a number of grounds, including but not limited to the reasons outlined above for all of the claims as well as the reasons described as applicable to them in particular.

In view of the foregoing, and the totality of the arguments in the record, Appellants request withdrawal of the rejection under 35 U.S.C. § 103 as to all of the claims.

CONCLUSION

For the reasons set forth above, Appellants respectfully request that the rejections of claims 9, 11-17, and 21-58 be withdrawn.

An attached Claims Appendix (viii) contains a copy of the claims under appeal.

An attached Evidence Appendix (ix) contains a copy of the various items of evidence cited above. These items are listed on the first two pages of the Evidence Appendix, along with a statement setting forth where in the record each item of evidence was entered in the record by the Examiner, as required under 37 CFR §41.37(c)(ix).

Appellants have also attached a Related Proceedings Appendix (x) as required, but it does not contain any subject matter.

Enclosed is a Petition for Extension of Time for two months and a Request for Oral Hearing. Also enclosed is a check for $450 for the Petition fee, a check for $500 for the Appeal Brief fee (as required under 37 C.F.R. § 41.20(b)(2)), and a check for $1000 for the Request for Oral Hearing fee (as required under 37 C.F.R. § 41.20(b)(3)). Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003.

Respectfully submitted,

Date: March 7, 2007

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(viii) Appendix of Claims

9. A method for reducing the frequency and/or intensity of chronic obstructive pulmonary disease (COPD) exacerbations experienced by a patient suffering from COPD, which method comprises administering to the patient via inhalation (i) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a second active ingredient which is budesonide, wherein_the method is effective to reduce the frequency and/or intensity of exacerbations in the patient, the first and second active ingredients are administered simultaneously, and the molar ratio of (a) formoterol in the first active ingredient to (b) the second active ingredient is from 1:555 to 2:1.

11. A method according to claim 9, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.

12. A method according to claim 9, wherein the first active ingredient is formoterol fumarate dihydrate.

13. A method according to claim 9, wherein the molar ratio is from 1:133 to 1:6.

14. A method according to claim 13 wherein the molar ratio is from 1:70 to 1:4.

15. A method according to claim 9, wherein the first and second active ingredients are provided in powder form.

16. A method according to claim 15 wherein the first and second active ingredients are formulated as powder particles having a mass median diameter of less than 10 μm.

17. A method according to claim 9 wherein the first and second active ingredients are provided in the form of an admixture.

21. A method according to claim 9 wherein the first active ingredient is administered to the patient in one or more unit doses per day, the amount of formoterol delivered to the patient by each unit dose of the first active ingredient being from about 2 to 120 nmol.

22. A method according to claim 21 wherein the amount of formoterol delivered to the patient by each unit dose of the first active ingredient is from about 7 to 70 nmol.

23. A method according to claim 9 wherein the second active ingredient is administered to the patient in one or more unit doses per day, the amount of budesonide delivered to the patient by each unit dose being from about 0.1 to 5 μmol.

24. A method according to claim 23 wherein the amount of budesonide delivered to the patient by each unit dose is from about 0.15 to 4 μmol.

25. A method according to claim 12 wherein the formoterol fumarate dihydrate is administered to the patient in one or more unit doses per day, the amount of formoterol fumarate dihydrate delivered to the patient by each unit dose being from about 1 to 50 μg.

26. The method of claim 9, further comprising monitoring the number of exacerbations experienced by the patient over a period of 12 months of treatment.

27. The method of claim 9, wherein the first active ingredient is administered in the form of one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 4.5 μg of formoterol fumarate dihydrate to the patient; and the second active ingredient is administered in the form of one or more unit doses of budesonide, each unit dose of budesonide delivering 160 μg of budesonide to the patient.

28. The method of claim 27, wherein the unit doses of both the formoterol fumarate dihydrate and the budesonide are administered one to four times per day.

29. The method of claim 9, wherein the first and second active ingredients are administered together from a pressurized metered dose inhaler (pMDI).

30. The method of claim 9, wherein at least one of the first and second active ingredients is formulated in a propellant comprising one or both of P227 (heptafluoropropane) and P134(a) (tetrafluoroethane).

31. The method of claim 12, wherein the first and second active ingredients are provided in admixture.

32. The method of claim 31, wherein the first and second active ingredients are in powder form.

33. The method of claim 32, wherein the first and second active ingredients are administered in admixture in the form of unit doses, each unit dose delivering to the patient 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide.

34. The method of claim 33, wherein the patient is administered one to four of the unit doses per day.

35. The method of claim 32, wherein the first and second active ingredients are administered in admixture in the form of unit doses, each unit dose delivering to the patient 9 μg formoterol fumarate dihydrate and 320 μg budesonide.

36. The method of claim 35, wherein the patient is administered one or two of the unit doses per day.

37. The method of claim 9, wherein the first active ingredient is in the form of one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 4.5 μg of formoterol fumarate dihydrate to the patient; and the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered in the form of one or more unit doses of budesonide, each unit dose of budesonide delivering 80 μg of budesonide to the patient.

38. The method of claim 37, wherein the unit doses of both the first active ingredient and the second active ingredient are administered one to four times per day.

39. The method of claim 9, wherein the first active ingredient is administered in the form of one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 9 μg of formoterol fumarate dihydrate to the patient; and the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered in the form of one or more unit doses of budesonide, each unit dose of budesonide delivering 160 μg of budesonide to the patient.

40. The method of claim 39, wherein the unit doses of both the first active ingredient and the second active ingredient are administered once or twice per day.

41. A method for the treatment of a patient suffering from COPD, which method comprises administering to the patient via inhalation (i) a daily dose of a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, the daily dose of the first active ingredient delivering 2 to 120 nmol of formoterol to the patient; and (ii) a daily dose of a second active ingredient that is budesonide, the daily dose of the second active ingredient delivering 45 to 2200 μg of budesonide to the patient, wherein the first active ingredient, which may be separate from or in admixture with the second active ingredient, is administered simultaneously with the second active ingredient, and wherein the daily dose of each active ingredient is administered in one to four divided doses per day.

42. The method of claim 41, wherein each daily dose of the first active ingredient is administered as one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 9 μg of formoterol fumarate dihydrate to the patient; and each daily dose of the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered as one or more unit doses of budesonide, each unit dose of budesonide delivering 320 μg of budesonide to the patient.

43. The method of claim 42, wherein the unit doses of both the formoterol fumarate dihydrate and the budesonide are administered once or twice per day.

44. The method of claim 41, wherein each daily dose of the first active ingredient is administered as one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 4.5 μg formoterol fumarate dihydrate to the patient; and each daily dose of the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered as one or more unit doses of budesonide, each unit dose delivering 80 μg of budesonide to the patient.

45. The method of claim 41, wherein each daily dose of the first active ingredient is administered as one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 9 μg formoterol fumarate dihydrate to the patient; and each daily dose of the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered as one or more unit doses of budesonide, each unit dose delivering 160 μg of budesonide to the patient.

46. The method of claim 45, wherein the unit doses of both the first active ingredient and the second active ingredient are administered once or twice per day.

47. The method of claim 41, wherein each daily dose of the first active ingredient is administered as one or more unit doses of formoterol fumarate dihydrate, each unit dose delivering 4.5 µg formoterol fumarate dihydrate to the patient; and each daily dose of the second active ingredient, which may be separate from or in admixture with the first active ingredient, is administered as one or more unit doses of budesonide, each unit dose delivering 160 µg of budesonide to the patient.

48. The method of claim 41, wherein the first and second active ingredients are administered together from a single pMDI.

49. The method of claim 41, wherein at least one of the first and second active ingredients is formulated in a propellant comprising one or both of P227 and P134(a).

50. The method of claim 41, wherein the method produces a reduction in frequency or intensity of COPD exacerbations in the patient.

51. The method of claim 41, wherein the method produces an improvement in FEV_1 in the patient.

52. A method for treating a patient suffering from COPD, which method comprises administering to the patient, via inhalation from a pMDI, a composition comprising (i) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; (ii) a second active ingredient that is budesonide; and (iii) propellant P227, wherein the molar ratio of (a) formoterol in the first active ingredient to (b) the second active ingredient is from 1:70 to 1:4.

53. The method of claim 52, wherein the patient inhales 4.5 or 9.0 µg formoterol fumarate dihydrate once or twice per day and 80 or 160 µg budesonide once or twice per day.

54. The method of claim 52, wherein the method produces a reduction in frequency or intensity of COPD exacerbations in the patient.

55. The method of claim 52, wherein the method produces an improvement in FEV_1 in the patient.

56. A method for the treatment of a patient suffering from COPD, which method comprises administering formoterol fumarate dihydrate and budesonide to the patient via inhalation, wherein the formoterol fumarate dihydrate and budesonide are administered simultaneously and optionally in admixture; the amount of formoterol fumarate dihydrate inhaled by the patient is 18 μg per day; and the amount of budesonide inhaled by the patient is 640 μg per day.

57. A method for the treatment of a patient suffering from COPD, which method comprises administering to the patient via inhalation (i) a daily dose of a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, the daily dose of the first active ingredient delivering an amount of formoterol to the patient per day that is equivalent to the amount delivered when 18 μg of formoterol fumarate dihydrate per day is delivered to the patient; and (ii) a daily dose of a second active ingredient that is budesonide, the daily dose of the second active ingredient delivering 640 μg of budesonide to the patient per day, wherein the first active ingredient is optionally in admixture with the second active ingredient, and the two active ingredients are administered simultaneously.

58. A method for the treatment of a patient suffering from COPD, which method comprises administering formoterol fumarate dihydrate and budesonide to the patient via inhalation, wherein the formoterol fumarate dihydrate and budesonide are administered simultaneously, and optionally in admixture, in one to four unit doses per day; the amount of formoterol fumarate dihydrate delivered to the patient by each unit dose of formoterol fumarate dihydrate is 4.5 μg; and the amount of budesonide delivered to the patient by each

unit dose of budesonide is 160 μg.

(ix) Evidence Appendix

Item 1. (1 page) Page 7 only of "GOLD: Global Initiative for Chronic Obstructive Lung Disease; Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease," based on April 1998 NHLBI/WHO Workshop, pages 1-100 (2004 update). This reference was submitted in its entirety and cited in an information disclosure statement, which was initialed and entered in the record by the Examiner with the Advisory Action dated December 4, 2006.

Item 2. (2 pages) Rabe, "Combination Therapy for Chronic Obstructive Pulmonary Disease," *Eur. Respir. J.* 22:874-875, 2003. This reference was cited in an information disclosure statement, and was initialed and entered in the record by the Examiner with the non-final Office Action dated June 18, 2004.

Item 3. (4 pages) The Merck Manual, 16th ed., s.v. "Chronic Airways Obstructive Disorders," pages 658-659, 1992. This reference was cited by the Examiner in a form PTO-892 and was entered in the record with the final Office Action dated June 15, 2006.

Item 4. (6 pages) Declaration of Jan Trofast under 37 CFR § 1.114(c) submitted March 1, 2004. This Declaration was acknowledged and entered in the record by the Examiner at pages 4-5 of the non-final Office Action dated June 18, 2004.

Item 5. (1 page) Smeenk *et al.*, "Opportunistic Lung Infection in Patients with Chronic Obstructive Pulmonary Disease; a side effect of Inhalation Corticosteroids," *Nederlands Tijdschrift voor Geneeskunde* 140:94-98, 1996 (Netherlander language); English Abstract only. This reference was cited by the Examiner in a form PTO-892 and was entered in the record with the non-final Office Action dated January 29, 2002.

Item 6. (5 pages plus 5 journal articles labeled Exhibits A-E) Declaration of Jan Trofast under 37 CFR § 1.132 submitted April 25, 2002. Exhibit A is Jeffrey, *Thorax* 53:129-136, 1998; Exhibit B is Pauwels *et al., New Eng. Jour. Med.* 340:1948-1953, 1999; Exhibit C is Niewoehner *et al., New Engl. Jour. Med.* 340:1941-1945, 1999; Exhibit D is Barnes, *Lancet* 351:766-780, 1998; and Exhibit E is Norman, *Drug News Perspect.* 11:431-437, 1998. The Declaration was acknowledged and entered in the record by the Examiner at page 2 of the non-final Office Action dated July 30, 2002.

Item 7. (8 pages) Declaration of Christer Hultquist submitted December 13, 2002. Item 7 includes Appendices 1 and 2. This Declaration was acknowledged and entered in the record by the Examiner at page 2 of the final Office Action dated January 29, 2003.

Item 8. (15 pages) Declaration of Jan Trofast submitted November 4, 2005. Item 8 includes Appendices 1-9. This Declaration was acknowledged and entered in the record by the Examiner at page 8 of the final Office Action dated June 15, 2006.

Item 9. (8 pages) Calverley *et al.*, "Maintenance Therapy with Budesonide and Formoterol in Chronic Obstructive Pulmonary Disease" *Eur. Resp. J.* 22:912-919, 2003. This reference was cited in an information disclosure statement, and was initialed and entered in the record by the Examiner with the non-final Office Action dated June 18, 2004.

Item 10. (5 pages) Vestbo *et al.*, "Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial" *Lancet* 353:1819-1823, 1999. This reference was cited in an information disclosure statement, and was initialed and entered in the record by the Examiner with the Advisory Action dated December 4, 2006.

Item 6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Carl-Axel Bauer et al.	Art Unit	: 1614
Serial No.	:	Examiner	: R. Cook
Filed	: November 13, 2001		
Title	: NEW USE FOR BUDESONIDE AND FORMOTEROL		

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF JAN TROFAST UNDER 37 CFR §1.132

I, Jan Trofast, declare as follows:

1. I am a co-inventor of the invention claimed in this application.

2. The invention claimed in this application features a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient, via inhalation, (i) formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) budesonide, the molar ratio of (i) to (ii) being from 1:2500 to 12:1.

3. I have read the Office Action mailed May 10, 2001 in the parent application (USSN 09/670,457).

4. COPD refers to a group of disorders characterized by a progressive and generally irreversible limitation of airflow. COPD is a common disease in industrialized countries (for example, about 6 % of the men and 4 % of the women over 45 years in the UK are affected) and is responsible for a considerable morbidity and mortality. Most of the patients are smokers. The

CERTIFICATE OF DELIVERY BY HAND

I hereby certify that this correspondence is being delivered by hand on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

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~~CERTIFICATE OF MAILING BY FIRST CLASS MAIL~~

~~I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.~~

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two most important conditions associated with COPD are chronic bronchitis and emphysema. Patients with chronic bronchitis exhibit frequent exacerbations due to recurrent infections.

5. Current treatment of COPD is often unsatisfactory. At present, COPD is often treated only in its more developed stages using a variety of inhaled or orally administered bronchodilators or inhaled anti-cholinergic agents. The problem with these treatments is that none of them has been regarded as effective. Smoking cessation has been shown to decrease the rate of decline in lung function, but the success of smoking-cessation programs is limited.

6. Airway inflammation in COPD differs from such inflammation in asthma. (Jeffery PK, Structural and Inflammatory Changes in COPD: a comparison with asthma. Thorax 1998:53:129-36; attached as Exhibit A). The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. However, their usefulness in COPD is much less certain. Around the time of Applicants' invention, researchers were investigating the use of inhaled glucocorticoids such as budesonide in treating COPD. The results, discussed below, generally indicated that inhaled glucocorticoids were much less effective in treating COPD than in treating asthma.

7. One study reported that the overall effect of three years of treatment with budesonide on the forced expiratory volume (FEV) of patients with mild COPD was "quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma.... The small, overall, one-time beneficial effect on pulmonary function ... must be balanced against the risk of local and systemic side effects." Benefits were found to be only short-term, with no appreciable effect on the long-term progressive decline in lung function. (Pauwels et al., "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," The New England Journal of Medicine, 340:25, pp. 1948-1953, June 24, 1999; attached Exhibit B.)

8. Another study found that the benefits of systemic glucocorticoids in treating acute exacerbations of COPD were much smaller than the benefits of glucocorticoids in the treatment

of severe exacerbations of asthma. (Niewoehner, "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease," The New England Journal of Medicine, 340:25, pp. 1941-1947, June 24, 1999; attached as Exhibit C.)

9. Several articles at the time mentioned that the current treatments for COPD, including treatment with inhaled steroids, were unsatisfactory, and that new treatments were required. (See, e.g., "Inhaled Steroids in COPD," The Lancet, Vol. 351, pp. 766-767, March 14, 1998, and "COPD: New Developments and Therapeutic Opportunities," Peter Norman, Drug News Perspect 11(7), September 1998; attached as Exhibits D and E, respectively.)

10. In view of this lack of enthusiasm in the field for treatment with budesonide, and also in view of the recognition in the art that asthma and COPD respond differently to treatment with budesonide, it would not have been obvious to the artisan that Carling's composition would be effective in the treatment of COPD. Moreover, in view of the great need for an effective treatment for COPD, if it had been obvious to Carling himself that his composition would have been effective in treating COPD, surely he would have mentioned this in his own disclosure.

11. The Examiner states that, in the absence of unexpected results, it would have been obvious in view of the cited references (U.S. Patent No. 5,795,564 and CA 126:259329) to use budesonide and formoterol together to treat COPD. Applicants respectfully disagree, for the reasons discussed above, and also because Applicants have in fact obtained unexpected results.

12. About 800 patients with moderate to severe COPD were enrolled in a clinical trial. They were divided into four equal groups taking, respectively: budesonide/formoterol (as fumarate dihydrate)(2 x 160/4.5 μg bid, single inhaler), budesonide (2 x 200 μg bid), formoterol (as fumarate dihydrate) (2 x 4.5 μg bid) and a placebo for a period of 12 months. There was a significantly larger number of discontinuations in the placebo group than in the treated groups. The patients were monitored for severe exacerbations, and were tested at each clinical visit (8

times) for Forced Expiratory Volume (FEV_1). These parameters are typically used in evaluating the condition of a patient suffering from COPD.

13. A statistical analysis of the results of this study provided the following data:

Reduction in severe exacerbations (P-value):

Budesonide/formoterol against placebo	0.035
Budesonide/formoterol against formoterol	0.043
Budesonide/formoterol against budesonide	0.385

Improvement in forced expiratory volume (FEV_1) (P-value):

Budesonide/formoterol against placebo	< 0.001
Budesonide/formoterol against budesonide	< 0.001
Budesonide/formoterol against formoterol	0.487

The reduction of severe exacerbations was significantly ($p<5\%$) greater for the patients treated with the budesonide/formoterol combination than for the placebo or the formoterol-treated groups. The study indicates that the number of exacerbations was 24 % lower for the patients treated with the combination than for the patients who received a placebo, and 23 % lower in comparison with formoterol-treated group.

The Forced Expiratory Volume of patients treated with the combination was significantly better ($p<0.1\%$) for the patients treated with the combination than for the placebo or budesonide-treated groups.

14. Together, the results obtained for these parameters indicate a significant improvement in both of the measured parameters for the budesonide/formoterol-treated patients, as compared to the patients treated with either budesonide alone or formoterol alone, over the 12-month period. Thus, the results of this study indicate, unexpectedly, that it is possible to treat even moderate to severe COPD patients with excellent, long-term results using the claimed method.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 30 Nov. 2001

Jan Trofast

Figure 2 Scanning electron micrograph of the surface of human bronchial mucosa showing a field of cilia with flakes of mucus at their tips.

Figure 3 Scanning electron micrograph of bronchial surface showing the experimental effects of subacute exposure to cigarette smoke: there is a near complete sheet of mucus.

both mechanisms are effective in clearing large proximal airways (down to about the sixth generation of branching). Sputum and respiratory tract secretions are a mixture of constituents including glycoproteins, glycosaminoglycans, lipids and transudate. Respiratory tract secretions normally amount to less than 100 ml/day[15] and are thought to consist primarily of glycosaminoglycans.[16 17] Chronic irritation by pollutants causes alterations in the biochemistry and flow of mucus and in the number and activity of secretory cells – that is, there is an enlargement of the mass of submucosal gland (by an increase in both the number and size of its cells) and an increase in the number of mucous cells (goblet cells) in the surface epithelium. Mucous gland enlargement and hyperplasia of goblet cells are the historical hallmarks of chronic bronchitis.[18] The changes to secretory cells are also reported in asthma. However, in contrast to chronic bronchitis, the airways in fatal asthma are occluded by tenacious plugs of exudate and mucus, there is patchy loss of surface epithelium, relatively uniform thickening and hyaline appearance of its reticular basement membrane, marked enlargement of the mass of bronchial smooth muscle and bronchial vessel dilatation, congestion, and oedema.[11 19]

The normal presence of a gel-like mucus is essential to mucociliary clearance – in normal healthy subjects the mucus is present as discrete flakes (fig 2) but in subjects with smokers' bronchitis it is thought to be present as a continuous sheet or "blanket" (fig 3). Whilst bronchial goblet cell hyperplasia may be a feature of both chronic bronchitis and asthma, the appearance and increase of goblet cells in the small airways – that is, small bronchi and bronchioli of less than 2 mm diameter – where goblet cells are normally absent or sparse (a change referred to as mucous metaplasia) is a key alteration that contributes to small airways disease and the development of COPD.[20 21] In the large airways disproportionate reduction of serous acini of the submucosal glands which contain lysozyme, lactoferrin, and a small molecular weight antiprotease tends to favour bacterial colonisation. This is reported not to occur in asthma.[22] Other epithelial changes in chronic bronchitis may include atrophy,[23] focal squamous metaplasia,[24] ciliary abnormalities,[25] and decreases in both ciliated cell number and mean ciliary length.[26–28] Loss of mucociliary clearance due to alterations in the flow/adhesive properties of mucus or to ciliary damage results in pooling of secretions. These pooled secretions support the growth of bacteria (fig 4) which release products known to damage both cilia and the underlying epithelial cells. Once damaged, the epithelial cells are sloughed and only then may bacteria be found directly adherent to them (fig 5).

SMALL AIRWAYS (CHRONIC BRONCHIOLITIS)

Measurement of sputum only reflects secretions obtained by cough from about the first six generations of airway branching. Mucus produced at this proximal site probably serves to protect the more distal and respiratory portions of the lung. However, mucus produced inappropriately in bronchioli by the process of mucous metaplasia has a number of detrimental effects including a reduction of bronchiolar antiproteases leading to proteolytic digestion and the development of centrilobular emphysema.

As the cross sectional area of the bronchiolar zone of the lung is normally large in relation to the bronchial divisions,[29] breathlessness and airflow limitation due to small airway disease are detectable only late in the course of the condition. This means that, once detected,

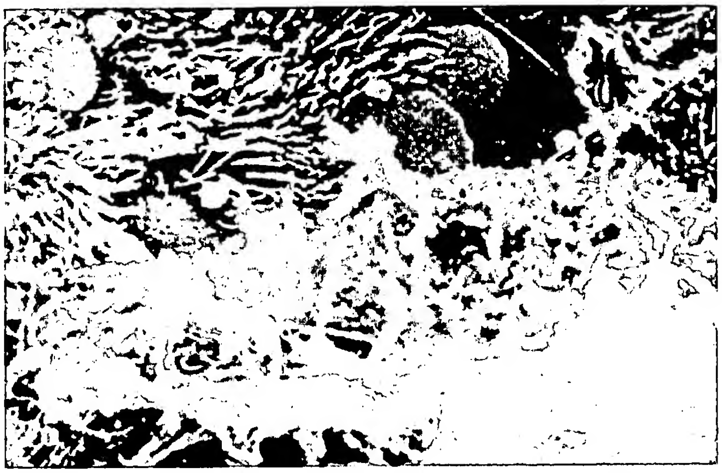

Figure 4 Scanning electron micrograph of human airway surface but not the underlying airway epithelial cells showing colonisation of airway mucus by bacteria (Pneumococcus sp).

Figure 5 Scanning electron micrograph of surface mucosa illustrating the effects of bacterial (Haemophilus sp) toxins on the epithelium; ciliated and non-ciliated cells are damaged and sloughing and now bacteria have attached to their cell membranes.

Figure 6 Bronchial cast of human small airways illustrating the marked focal constriction of one airway branch in COPD (courtesy of Professor J Bignon).

relatively severe progressive changes are already well established. However, inflammation in small airways occurs relatively early and may be detected physiologically well before the age of 30 years.[7 30] The small airway defect is characterised by persistent airflow limitation which may show progressive deterioration in the absence of emphysema. Whilst the site of the lesion and diagnosis is, as yet, difficult to pinpoint by lung function, experimental physiologists have indicated that the dominant site lies in small bronchi and bronchioli of less than 3 mm diameter.[31 32]

Histologically one of the most consistently observed early effects of cigarette smoke is a marked increase in the number of macrophages and neutrophils in the airways of both man and experimental animals. The increase is seen also within the lung interstitium and alveolar space and can be detected in bronchoalveolar lavage (BAL) fluid.[33 34] The associated early smoking-related structural changes have been described in studies comparing lungs of young smokers and controls of similar age in a group who had experienced sudden non-hospital deaths.[20 33 35 36] In these and more severely affected patients the structural changes include mucous metaplasia, bronchiolar smooth muscle hypertrophy, mural oedema, peribronchiolar fibrosis, and an excess of airways less than 400 µm in diameter.[20 33 35 36] It is suggested that the primary lesion is persistent and progressive inflammation then leads to peribronchiolar fibrosis. The resultant narrowing of small bronchioli has been convincingly demonstrated by Bignon and colleagues (fig 6).[37] The peribronchiolar inflammation (fig 7) and fibrosis may predispose to the development of centrilobular emphysema and may be responsible for the subtle abnormalities detected by lung function. Associated loss of alveolar attachments to the airway perimeter (fig 8) contributes to loss of elastic recoil and favours increased tortuosity and early closure of bronchioli during expiration.[38–40]

In bronchioli, non-ciliated secretory and ciliated cells are the main cell types[41 42] and, of them, the Clara cell is the major secretory cell type as well as the progenitor cell from which ciliated and mucous cells may develop. It has been suggested that the Clara cell normally produces both a hypophase component of bronchiolar surfactant[43] and a low molecular weight protease inhibitor (*syn* antileukoprotease or bronchial mucosal protease inhibitor[44]). The latter is the main anti-elastase screen in sputum and normally prevents autolysis of airway tissues.[45] In smokers Clara cells are replaced by mucous cells[21] and mucus appears in peripheral airways and its secretion is abnormally increased therein.[46] The increase in mucus at this distal site is difficult to clear by cough. In addition, its replacement of the normal surfactant lining leads to an abnormally high surface tension and small airway instability and also predisposes to early airway closure during expiration.[47] In addition, replacement of Clara cells and their anti-elastase secretion predisposes the small airway to proteolytic digestion; such changes in respiratory bronchioli

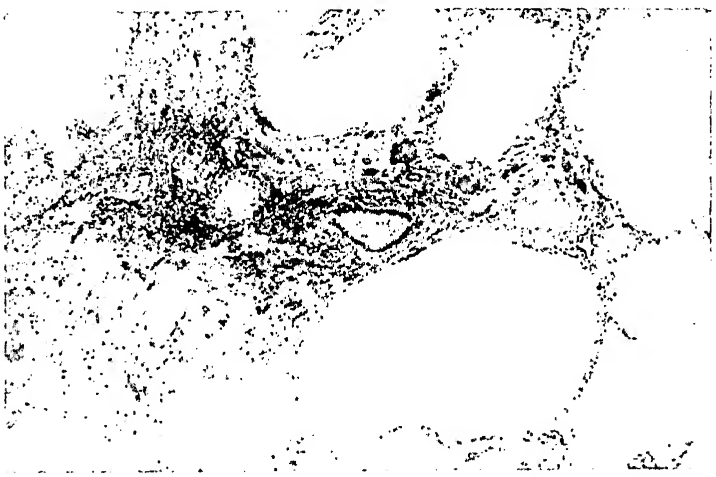

Figure 7 Histological section of alveolar region in a case of COPD in which there are enlarged alveolar spaces surrounding a small airway with marked peribronchiolitis. Stain: haematoxylin and eosin (courtesy of Professor B Corrin).

Figure 8 Section of emphysematous lung in which there is destruction of alveolar attachments to the bronchiolar wall, resulting in its tortuous appearance and early collapse during expiration. Stain: haematoxylin and eosin.

may underlie the development of centriacinar emphysema.

EMPHYSEMA

The early changes of emphysema have been thought to include subtle disruption to elastic fibres with accompanying loss of elastic recoil, bronchiolar and aveolar distortion (see fig 8), and the appearance of fenestrae which enlarge,[48 49] an alteration which has been referred to as "microscopic" emphysema (fig 9). These biochemical and microscopic changes lead to loss, by destruction of the elastic framework, of the interalveolar septa and the macroscopic appearance of spaces of more than 1 mm in diameter. Recent data have shown that this destructive process is accompanied by a net increase in the mass of collagen which suggests that, contrary to the current internationally accepted definition (see above), there is active alveolar wall fibrosis in the tissue which remains even in otherwise emphysematous lungs.[50]

Two main morphological forms of emphysema have been described. They are distinguished anatomically by the region of the acinus which is destroyed. Centriacinar (or centrilobular) emphysema is characterised by focal destruction restricted to respiratory bronchioli and the central portions of the acinus, each focus surrounded by areas of grossly normal lung parenchyma. This form of emphysema is usually more severe in the upper lobes of the lung (fig 10). Panacinar (or panlobular) emphysema involves destruction of the walls, in a fairly uniform manner, of all the air spaces beyond the terminal bronchiolus. The panacinar form is characteristic of patients who develop smoking-related emphysema relatively early in life and, in contrast to the centriacinar form, has a tendency to involve the lower lobes more than the upper. In the familial form of panacinar emphysema it is usually associated with deficiency of alpha$_1$-antitrypsin[51] which normally protects the respiratory region by forming a highly effective anti-elastase screen. These distinct morphological forms are thought to have distinct functional properties.[52]

Epidemiological studies have demonstrated a significant relationship between cigarette smoking and severity of emphysema[53] but the mechanism(s) by which cigarette smoke causes such damage is still the subject of much speculation. The working hypothesis has been that emphysema is the result of an imbalance between proteolytic enzymes and protease inhibitors in the lung, favouring an excess of enzyme and, in particular, elastases. In addition, the imbalance between oxidants and antioxidants also contributes by allowing an excessive oxidant burden to degrade the normal protease inhibitor screen.[54 55] The proposed mechanism involves interactions between cigarette smoke, alveolar macrophages, chemoattractants, neutrophils, elastases, endogenous and exogenous oxidants, protease inhibitors, antioxidants, and lung connective tissue, primarily elastin, which undergoes repeated destruction, synthesis, and degradation.[56]

Whilst the major pathological changes of COPD are thought to occur in the airways and lung parenchyma in patients with advanced COPD, changes also occur to the pulmonary circulation, the right heart, and respiratory muscles.[57] With alveolar hypoxia the medial vascular smooth muscle of pulmonary arterioles extends distally to vessels that normally lack muscle and there is intimal thickening. In addition, loss of the vascular bed occurs as a consequence of emphysema. Right ventricular enlargement due to dilatation and/or hypertrophy is not uncommon and atrophy of the diaphragm occurs in some cases of COPD. Whilst emphysema and right ventricular hypertrophy are common in COPD, both are uncommon findings in asthma.

Cellular infiltrate

Niewoehner and co-workers[33] and Cosio and colleagues[20] were among the first to describe the inflammation of the respiratory region in smokers dying suddenly: inflammation in bron-

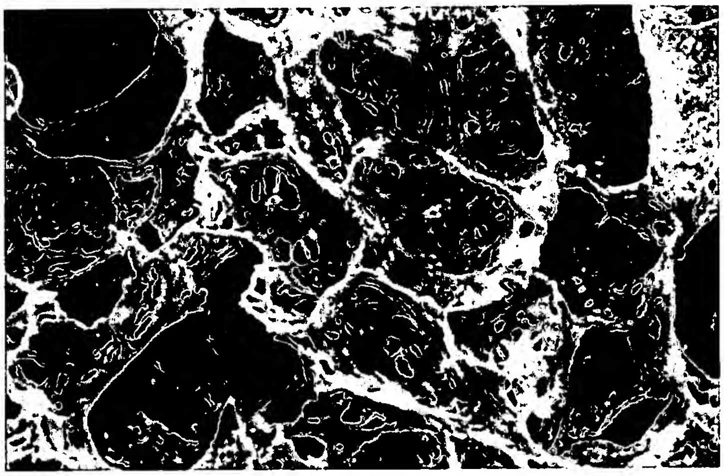

Figure 9 Scanning electron micrograph of a human lung in which there is "microscopic" emphysema; the alveolar walls are peppered by fenestrae too small to be seen by the naked eye. Such early lesions probably result in loss of lung elastic recoil.

Figure 10 Gross appearance of the cut surface of a lung in which the centriacinar emphysema is restricted to the upper aspects of each lobe (courtesy of Professor B Heard).

chioles and a respiratory bronchiolitis and alveolitis consisting of pigmented macrophages.[58] These inflammatory changes to small airways appear to be related to clinical airflow obstruction in patients with COPD.[31 59 60] The destruction of the respiratory zone in emphysema is also considered to be the result of an inflammatory reaction, much of this centred on respiratory bronchioli and the alveolar wall and largely initiated by products of inhaled tobacco smoke which recruit neutrophils to the lung.[12 55 61] The average diameter of circulating neutrophils is 7.0 µm which necessitates their deformation as they squeeze through capillary segments of 5 µm diameter. Neutrophil traffic through the capillaries of the lung is normally slower – that is, there is a higher transit time – than that of red blood cells as they are 700 times less deformable than red blood corpuscles.[61] Recent studies with radioactively labelled neutrophils have shown that the normal delay in neutrophil transit is further exaggerated, transiently, even in healthy subjects during smoking.[62] Exposure of neutrophils to cigarette smoke in vitro and in vivo results in decreased deformability associated with polymerisation of actin microfilaments.[61 63] This is the probable mechanism of the observed cigarette smoke induced increase in neutrophil transit time in the periphery of the lung. More recently lymphocytes have been found to form a significant component of the alveolar wall inflammatory infiltrate in patients with COPD.[64]

Inflammatory cells also infiltrate the bronchial mucosa of smokers and these relatively large airways have been the focus of recent biopsy studies conducted in volunteers using the flexible fibreoptic bronchoscope. The biopsy studies of the airways of smokers are of particular interest as they allow comparison with the biopsy changes reported in asthma. It is already known that in patients with atopic and non-atopic asthma there is an inflammatory infiltrate which comprises activated (CD25+), T helper (CD4+) lymphocytes and activated (EG2+) eosinophils associated with gene expression and secretion of interleukins (IL)-4 and IL-5, IL-10, and the pro-inflammatory cytokines GM-CSF and TNF-α.[65–71] The production of IL-4 and IL-5 but not IL-2 and interferon γ is referred to as the T helper type 2 (Th2) phenotype.

Electron microscopic and immunohistochemical techniques are only just beginning to be applied to examine the nature of the inflammatory infiltrate in COPD. In bronchial biopsy specimens taken from subjects with stable COPD and exacerbations of bronchitis there is evidence of inflammation (fig 11).[72–76] Similar to the periphery of the lung, bronchial mononuclear cells also appear to form a predominant cell type with scanty neutrophils (in the absence of an exacerbation of infection) and, in contrast to asthma, there are relatively few eosinophils; the mononuclear component comprises lymphocytes, plasma cells, and macrophages. Significant increases are reported in the numbers of CD45 (total leucocytes), CD3 (T lymphocytes), CD25 activated and VLA-1 (late activation) positive cells and of macrophages.[74] There is an increased number of tissue eosinophils compared with that found in normal healthy controls and it has been suggested that, in contrast to asthma, the tissue eosinophils found in COPD do not degranulate.[72] However, Saetta and coworkers found that the numbers of tissue eosinophils were only increased when there was an exacerbation of bronchitis.[76 77] The same group of workers, together with another, report increases in the cell surface adhesion molecules associated with such inflammation.[75 76] Our own recent study found few neutrophils and eosinophils in bronchial biopsy specimens from stable bronchitic smokers with or without COPD; as airflow limitation progressively worsened T lymphocytes and neutrophils in-

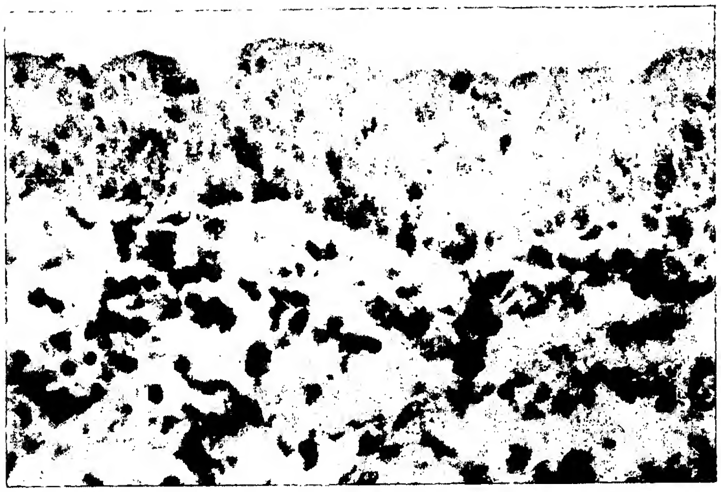

Figure 11 Histological section of a mucosal biopsy specimen taken by flexible fibreoptic bronchoscopy from a patient with an exacerbation of bronchitis. There are large numbers of CD45+ leucocytes infiltrating the subepithelial zone and fewer within the squamoid surface epithelium. (Immunostained by Dr Li using the APAAP technique and new fuchsin to stain the CD45+ cells red; biopsy specimen kindly obtained by Dr Saetta.)

Table 1 Fold increases (compared with healthy controls) in subjects with chronic bronchitis alone (CB) or with airflow limitation (CB+COPD) and atopic asthma

	CB	*CB+COPD*	*Asthma*
CD45+	2.2	2.3	2
CD3+	2.3	4.0	2
CD4+	±	2.8	2.5
CD8+	3	8.4	2
CD4:CD8+	1:4	1:2	3:1
Neutrophil	±	2.2	−1.5
Eosinophil	1.7	3.5	93
Macrophage	4.5	8.6	±

creased in the surface epithelium as did T lymphocytes and macrophages in the subepithelium. We found that it is the CD8+ lymphocyte subset which increases in number and proportion in COPD and the increase of CD8+ cells shows a significant association with decline in lung function.[10] This contrasts with the predominance and activation of the CD4+ T cell subset which is the characteristic change of mild atopic asthma. Interestingly, the high numbers of neutrophils found in lavage fluid from subjects with COPD[78] is not reflected in their numbers in the bronchial mucosa, at least in the subepithelial zone (often referred to as the lamina propria) which is the zone usually quantified in bronchial biopsies.[10 79]

The relative changes in each cell immunophenotype in chronic bronchitis or COPD, compared with their respective values in asthma and in normal healthy subjects, are summarised in table 1. Comparative studies of the distinct patterns of interleukin and cytokine gene expression in COPD and asthma are now urgently needed.

Concluding comments

Table 2 summarises the main distinctions between COPD and asthma. There is evidence of inflammation in both conditions but there are considerable differences in terms of the predominant phenotype and the site and functional consequences of such inflammation. At this stage in our knowledge the distinctions do not appear to be absolute. However, the author believes that by rigorous recordings of clinical data, careful application of the histological, cytological, immunological and molecular techniques now available, it will be possible for biopsy specimens of conducting airways to provide for differential diagnosis and the monitoring of either disease progression or responsiveness to treatment in both COPD and asthma.

Understanding the functional consequences of persistent inflammation and the ensuing structural damage/remodelling of airway and lung structure is important, difficult, and beyond the scope of this mini-review; for a succinct summary the reader is referred to an excellent article on the subject[13] and another which outlines the functional distinctions between the centrilobular and panlobular forms of emphysema.[52]

The hypersecretion of mucus which characterises chronic bronchitis has traditionally been considered to be irrelevant to the accelerated rate of decline in forced expiratory volume in one second (FEV_1) and to the disability of COPD.[80 81] However, even the role of this apparently innocuous feature of chronic bronchitis has recently been questioned as two relatively recent studies have reported that sputum volume is associated with an accelerated decline in FEV_1, increased hospital admission, and increased mortality.[82 83] This is in addition to the undoubted detrimental effects of mucus on the stability of small airways in COPD.[47]

Table 2 Simplified comparison of COPD and asthma

	COPD	*Asthma*
Airflow obstruction	Progressive deterioration of lung function (? reversible component)	Variable (± irreversible component)
Post mortem	Excessive mucus (mucoid/purulent), small airway disease, emphysema	Hyperinflation, airway plugs (exudate + mucus), no or little emphysema
Sputum	Macrophage, neutrophil (infective exacerbation)	Eosinophilia, metachromatic cells, Creola bodies
Surface epithelium	Fragility undetermined	Fragility/loss
Bronchiolar mucous cells	Metaplasia/hyperplasia	Mucous metaplasia is debated
Reticular basement membrane	Variable or normal	Homogeneously thickened and hyaline
Congestion/oedema	Variable/fibrotic	Present
Bronchial smooth muscle	Enlarged mass (small airways)	Enlarged mass (large airways)
Bronchial glands	Enlarged mass (increased acidic glycoprotein)	Enlarged mass (no change in mucin histochemistry)
Cellular infiltrate	Predominantly CD3, CD8, CD68, CD25, VLA-1 and HLA-DR + ve, mild eosinophilia (not degranulated?), mast cell increase	Predominantly CD3, CD4, CD25 (IL-2R) + ve, marked eosinophilia (EG2 + ve) (degranulated), mast cell increase (decrease in severe/fatal)
Cytokines (ISH)	GM-CSF protein ± IL-4 but not IL-5	IL-4 + IL-5 gene expression (Th2 profile)

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Inflammation appears to be present throughout the bronchial tree and respiratory portion of the lung in COPD. Similarly, there is widespread inflammation in asthma and tissue eosinophilia has recently been reported even in the alveolar walls.[84] The involvement of activated lymphocytes seems to be a common theme in both conditions yet the profound tissue eosinophilia of asthma does not appear in COPD. The predominant lymphocyte subsets in COPD and asthma appear to be distinct – that is, CD8+ and CD4+ cells, respectively (see table 1). Whilst there is consequent tissue destruction and remodelling in the periphery in COPD, there seems to be a contrasting trend towards involvement of relatively large proximal airways in asthma, particularly in respect of thickening of the reticular basement membrane and enlargement of the mass of bronchial smooth muscle – changes which do not occur in the large airways in COPD. The airflow limitation of COPD has two major recognised components: (1) increased resistance to airflow due mainly to the inflammatory and structural changes described in small airways and (2) loss of lung elastic recoil due to inflammation and alveolar wall destruction. It has been suggested that, when emphysema is mild to moderate, small airway lesions assume overriding importance, but if emphysema is "severe" it then dominates the contribution to decreased lung function.[59] Interestingly, a report by Hogg and co-workers found little relationship between macroscopic emphysema, severity score and FEV_1 and concluded that microscopic emphysema and small airway lesions were probably most responsible[85] for the deficit in lung function; this conclusion has received lively debate.[86]

As many life long smokers do not succumb to emphysema, constitutional factors are also likely to be important. Genetic deficiency of $alpha_1$-antitrypsin is well documented and smoking in this group clearly advances the onset of emphysema and accelerates its subsequent progression. Other genetic factors such as variation in cellular response to cytotoxicity, phagocytosis, and enzyme release may be important determinants of susceptibility to cigarette smoke.[87] More recently O'Shaughnessy and colleagues[10] have suggested that airway (and lung) susceptibility to the effects of cigarette smoke is likely to be greater in those individuals who already have a genetically determined low CD4/CD8+ cell ratio in their peripheral blood.[88] This is a novel explanation as to why only about 20% of smokers might succumb to its deleterious effects; however, the hypothesis requires testing and epidemiological proof.

Long term studies (soon to be reported) of the use of inhaled corticosteroids in COPD are currently in progress to test the hypothesis that airways inflammation bears a relationship with the rate of decline in FEV_1; if the relationship is a direct one then there should be a slowing of the rate of decline following attenuation of the inflammatory reaction. We await these results with interest.

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Item 6. Exhibit B

To [illegible] 9/11-01

LONG-TERM TREATMENT WITH INHALED BUDESONIDE IN PERSONS WITH MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE WHO CONTINUE SMOKING

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ABSTRACT

Background and Methods Although patients with chronic obstructive pulmonary disease (COPD) should stop smoking, some do not. In a double-blind, placebo-controlled study, we evaluated the effect of the inhaled glucocorticoid budesonide in subjects with mild COPD who continued smoking. After a six-month run-in period, we randomly assigned 1277 subjects (mean age, 52 years; mean forced expiratory volume in one second [FEV_1], 77 percent of the predicted value; 73 percent men) to twice-daily treatment with 400 μg of budesonide or placebo, inhaled from a dry-powder inhaler, for three years.

Results Of the 1277 subjects, 912 (71 percent) completed the study. Among these subjects, the median decline in the FEV_1 after the use of a bronchodilator over the three-year period was 140 ml in the budesonide group and 180 ml in the placebo group ($P=0.05$), or 4.3 percent and 5.3 percent of the predicted value, respectively. During the first six months of the study, the FEV_1 improved at the rate of 17 ml per year in the budesonide group, as compared with a decline of 81 ml per year in the placebo group ($P<0.001$). From nine months to the end of treatment, the FEV_1 declined at similar rates in the two groups ($P=0.39$). Ten percent of the subjects in the budesonide group and 4 percent of those in the placebo group had skin bruising ($P<0.001$). Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects, and the diagnoses were equally distributed between the groups.

Conclusions In persons with mild COPD who continue smoking, the use of inhaled budesonide is associated with a small one-time improvement in lung function but does not appreciably affect the long-term progressive decline. (N Engl J Med 1999;340:1948-53.)

CHRONIC obstructive pulmonary disease (COPD) is characterized by a progressive and largely irreversible limitation of airflow. Cigarette smoking is the principal risk factor, and smoking cessation has been shown to decrease the rate of decline in lung function,[1] but the success of smoking-cessation programs is limited.[2]

The decline in lung function in patients with COPD is related to the presence of inflammatory changes in the airways and lung parenchyma.[3] Airway inflammation in COPD differs from such inflammation in asthma.[4] Inhaled glucocorticoids are successfully used in asthma.[5] Some studies have shown an effect of inhaled glucocorticoids on airway inflammation in COPD.[6-9] In this study, we tested the hypothesis that regular treatment with the inhaled glucocorticoid budesonide would reduce the decline in lung function in patients with mild COPD who continued smoking.[10]

METHODS

Study Design

The study was a parallel-group, double-blind, placebo-controlled, randomized, multicenter study. Thirty-nine study centers in nine European countries (Belgium, Denmark, Finland, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) participated. Approval from regulatory and ethics committees was obtained at all centers. All subjects gave written informed consent.

The study started with a run-in phase consisting of a three-month smoking-cessation program. All subjects received extensive information about the health hazards of smoking and a starting package of nicotine gum. More extensive smoking-cessation programs were encouraged. In subjects who did not stop smoking, this phase was followed by a three-month period during which compliance with inhaled medication was assessed with the use of a placebo-containing dry-powder inhaler with a hidden mechanical counter. Subjects who continued smoking and were at least 75 percent compliant with the recommended treatment regimen were randomly assigned to twice-daily treatment with either 400 μg of budesonide (Pulmicort, Astra, Stockholm, Sweden) or placebo from a dry-powder inhaler (Turbuhaler, Astra) for three years. The primary outcome variable was the change over time in forced expiratory volume in one second (FEV_1) after use of a bronchodilator.

Subjects

Persons 30 to 65 years of age were eligible if they were currently smoking at least five cigarettes per day and had smoked cigarettes for at least 10 years or had a smoking history of at least 5 pack-

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*The other participants in the study are listed in the Appendix.

years. The FEV_1 after the use of a bronchodilator had to be between 50 percent and 100 percent of the predicted normal value,[11] and the ratio of prebronchodilator FEV_1 to slow vital capacity had to be less than 70 percent. The increase in FEV_1 after the inhalation of 1 mg of terbutaline from a dry-powder inhaler had to be less than 10 percent of the predicted normal value. The change in FEV_1 between the end of the first three-month period of the run-in phase and the end of the second had to be less than 15 percent. Subjects with a history of asthma, allergic rhinitis, or allergic eczema and those who had used oral glucocorticoids for more than four weeks during the preceding six months were excluded. The use of inhaled glucocorticoids other than the study medication, beta-blockers, cromones, or long-acting inhaled β_2-adrenergic agonists was not allowed.

Outcome Measures

Clinic Visits

The subjects were seen at the clinics every three months for spirometry and evaluation of smoking habits, compliance with medication, and safety-related variables. At selected centers, bone density was measured before treatment and after 6, 12, 24, and 36 months. Spine radiographs were obtained before and at the end of treatment.

Spirometry

Each center was supplied with a dry rolling-seal spirometer (model SMI III, Spirometrics, Auburn, Me.). The criteria of the American Thoracic Society[12] were used to determine FEV_1. All technicians attended an initial training session about the spirometer and the techniques to be used. Thereafter, regular visits were made by a monitor to check the calibration of the spirometer and to monitor the technique.

Spirometry was performed with the subject seated and wearing a nose clip. At recruitment and at the end of the study, slow vital capacity and FEV_1 were measured after at least 6 hours without inhaled bronchodilators and after 24 hours without oral bronchodilators. Three technically adequate and two reproducible maneuvers were required for the measurement of slow vital capacity and FEV_1. The largest values measured for slow vital capacity and FEV_1 were accepted, provided the second largest measurement was within 0.1 liter or 5 percent of the largest measurement. At all clinic visits, FEV_1 was obtained 15 minutes after the inhalation of 1 mg of terbutaline. Values were corrected for body temperature, ambient pressure, and water saturation and compared with the reference values of the European Community for Coal and Steel.[11]

Safety Studies and Serum Analysis

At each visit, subjects were specifically asked whether they had received a diagnosis of glucocorticoid-related diseases or conditions such as hypertension, bone fractures, posterior subcapsular cataracts, myopathy, or diabetes in the preceding period. The number of skin bruises larger than 50 mm in diameter on the volar side of the forearms was noted. All other adverse events were recorded. Serious adverse events were those that were judged by the investigators to constitute a hazard or handicap to the subject.

Lateral thoracic and lumbar spinal radiographs were obtained with standard values for target-to-film distance and centering. The films were sent to a central evaluator who was unaware of the treatment received and were analyzed according to a standardized computerized protocol. The presence or absence of vertebral fractures at base line was determined by comparing each subject's base-line vertebral height ratio with reference values. A new fracture was defined as a reduction of at least 20 percent, with an absolute decrease of at least 4 mm, in the height of any vertebral body.[13]

We measured the bone mineral density of the lumbar spine (L2 to L4), the femoral neck, Ward's triangle, and the trochanter by dual-energy x-ray absorptiometry with a densitometer (model QDR-1000, Hologic, Waltham, Mass., or model DPX-L, Lunar, Madison, Wis.). The quality of the instruments was assessed before and then monthly during the study by an external organization (Bona Fide, Madison, Wis.).

At randomization a blood sample was taken to test for IgE antibodies (Phadiatop, Pharmacia & Upjohn, Uppsala, Sweden).

Statistical Analysis

The sample size was based on an estimated standard deviation of the mean slope of the FEV_1 of 100 ml per year according to a previous study,[14] a withdrawal rate of 40 percent, and a power of 80 percent to detect a difference in treatment response of 20 ml per year. Data on the randomized subjects were analyzed on an intention-to-treat basis. Student's t-test was used to compare treatment groups with respect to normally distributed variables, and the Wilcoxon rank-sum test was used for other variables. The χ^2 test was used to compare categorical variables. Differences were assessed with two-sided tests, with an alpha level of 0.05.

Several models were used to assess the serial changes in the variables of interest in the longitudinal data. First, the change in the variables over time was examined graphically. Unweighted and weighted individual regression lines of the variable of interest against time were used to estimate the slopes for each subject. The weighted regression lines were estimated by linear-mixed-effects modeling,[15-17] with intercept and time in the model as both fixed and random effects. The slopes were calculated for various periods with stratification according to confounders, effect modifiers, or both, and were compared between treatment groups.

Piecewise linear regression analysis of FEV_1 against time within the budesonide group with a linear-mixed-effects model showed a best fit with one breakpoint after three or six months of treatment and fitted significantly better than a model that assumed linearity over the whole study period. The study period was therefore partitioned into two periods. The best fit was determined with the likelihood-ratio test for nested models or with Akaike's information criterion statistic.[18]

The data are presented either as absolute changes for all subjects who were in the study at a certain time or as unweighted slopes on the intention-to-treat population. These data are presented as median values, since their distribution was not normal.

RESULTS

From January 1992 to July 1993, 2157 potential subjects were recruited at the participating centers. Of these, 462 were found to be ineligible, and the remaining 1695 were enrolled in the smoking-cessation program, during which 169 (10 percent) stopped smoking. Of the remaining 1526 subjects, 1277 (84 percent) were compliant with the inhaled medication, continued smoking, and were randomly assigned to treatment (643 to placebo and 634 to budesonide). Nine hundred twelve subjects (71 percent) remained in the study for three years. During the study, 198 subjects were withdrawn because of noncompliance with the study procedures, 132 were withdrawn because of adverse events, and 35 were lost to follow-up, resulting in 176 withdrawals from the budesonide group and 189 from the placebo group. The reasons for withdrawal were similar in the two groups.

The base-line characteristics of the subjects in the two groups were similar (Table 1). The mean age was 52 years; 354 (27 percent) were women. The majority had been heavy cigarette smokers for many years and had mild, poorly reversible airflow limitation. The subjects had decreased their cigarette consumption during the six months before randomization (to a mean of 18.8 and 17.3 cigarettes per day, respec-

Table 1. Base-Line Characteristics of the 1277 Subjects at Enrollment.*

Characteristic	Placebo Group (N=643)	Budesonide Group (N=634)
Age (yr)	52.4±7.7	52.5±7.5
Male sex (%)	72.2	73.5
Height (cm)	173±9	173±8
Weight (kg)	73.9±13.6	74.7±13.2
Prebronchodilator FEV_1 (liters)	2.54±0.64	2.53±0.64
Prebronchodilator FEV_1 (% of predicted)	76.9±13.2	76.8±12.4
FEV_1:SVC	61.7±7.0	62.2±6.8
Reversibility of FEV_1 (% of predicted)†	2.8±3.6	2.9±3.8
Pack-years of smoking	39.2±20.1	39.4±20.1
Age when started smoking (yr)	16.4±3.8	16.8±3.9
Duration of smoking (yr)	35.9±8.2	35.8±7.8
Smoking at entry (no. of cigarettes/day)	22.4±11.1	22.0±9.8
Smoking at randomization (no. of cigarettes/day)	17.3±10.5	18.8±11.1
Positive Phadiatop test (%)‡	18.9	17.7

*Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in one second, and SVC slow vital capacity.

†This variable was measured after the inhalation of 1 mg of terbutaline.

‡The Phadiatop test detects the presence in serum of IgE antibodies to a panel of common inhalant allergens.

tively, in the budesonide and placebo groups at randomization). An increasing number of subjects in both treatment groups reported quitting smoking during the treatment period. At the end of the study, approximately 10 percent of the subjects (9.1 percent of the budesonide group and 11.2 percent of the placebo group) reported not smoking during the previous six months.

Changes in FEV_1 Values after Bronchodilator Use over Time

The changes in postbronchodilator FEV_1 over time differed between the two treatment groups (Fig. 1). The placebo group showed a linear decline in FEV_1 over time, with a slope of −65 ml per year. In the budesonide group, the FEV_1 improved over the first six months at a rate of 17 ml per year, as compared with a decline of 81 ml per year in the placebo group ($P<0.001$). However, the slopes from nine months to the end of treatment were similar in the two groups: −57 ml per year in the budesonide group and −69 ml per year in the placebo group ($P=0.39$) (Table 2). During that period, 55 percent of the subjects in the placebo group had a rapid decline in FEV_1 (more than 60 ml per year), as compared with 49 percent of the subjects in the budesonide group ($P=0.06$). In the 912 subjects who completed the study, the median decline in FEV_1 over the three-year period was 140 ml in the budesonide group and

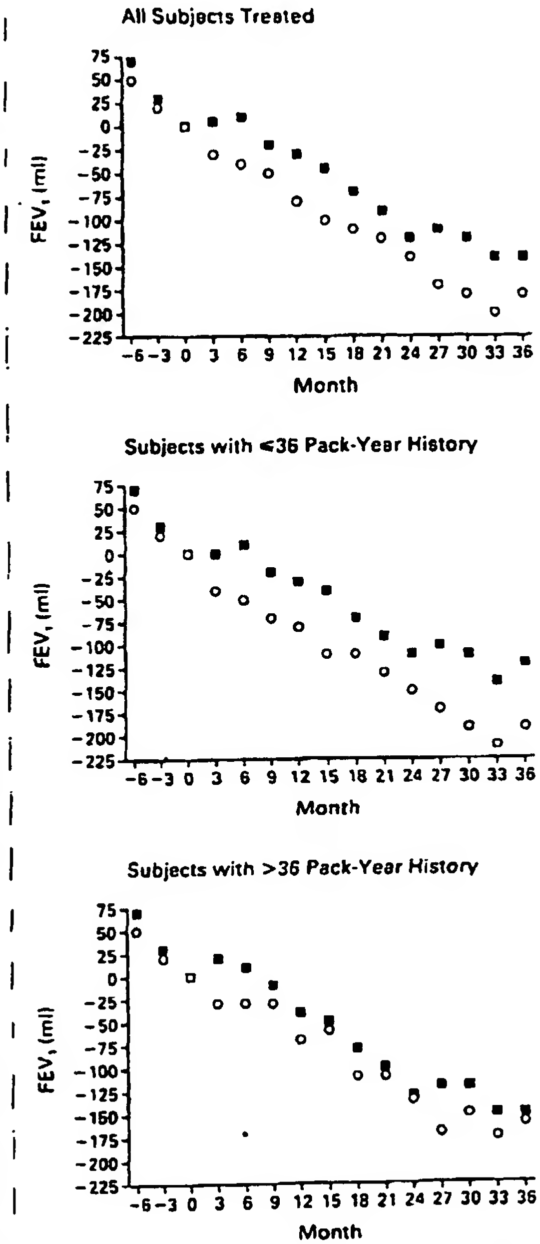

Figure 1. Median Change in Forced Expiratory Volume in One Second (FEV_1) as Compared with the Value at Randomization (Month 0) in the Placebo (O) and Budesonide (■) Groups.

The change is shown for all subjects treated, for subjects with a smoking history of 36 pack-years or less, and for subjects with a smoking history of more than 36 pack-years.

Table 2. Change in FEV_1 over Time in the Two Treatment Groups According to Smoking History.*

Smoking History	Treatment Period	Change in FEV_1†		P Value
		Placebo	Budesonide	
	mo	ml/yr		
All subjects	0–6	−81	17	<0.001
	9–36	−69	−57	0.39
Subjects with ≤36 pack-yr history	0–6	−90	30	<0.001
	9–36	−71	−47	0.08
Subjects with >36 pack-yr history	0–6	−70	0	0.57
	9–36	−65	−67	0.65

*Subjects were divided into two equal groups according to their smoking history at enrollment. The median was 36 pack-years. FEV_1 denotes forced expiratory volume in one second.

†The change is shown as the median of the FEV_1 slopes (in milliliters per year) during different parts of the study.

Table 3. Serious Adverse Events, Discontinuations Due to Adverse Events, Deaths, and Glucocorticoid-Related Side Effects.

Event*	Subjects with at Least One Adverse Event		P Value
	Placebo Group	Budesonide Group	
Serious adverse event — no.	161	177	0.37
Neoplasm	25	31	
Cardiovascular disorder	32	28	
Gastrointestinal disorder	15	17	
Respiratory disorder	14	17	
Musculoskeletal disorder	16	14	
Discontinuation due to adverse events — no.	62	70	0.51
Bronchial carcinoma	10	7	
Myocardial infarction	5	5	
Oropharyngeal candidiasis	0	8	
Coughing	4	3	
Urinary-bladder carcinoma	4	3	
Deaths — no.†	10	8	0.64
Glucocorticoid-related side effects			
Oropharyngeal candidiasis — no.	10	31	<0.001
Pharyngeal irritation or hoarseness — no.	28	46	0.04
New lumbar fractures			0.50
No. of subjects	3	5	
No. of fractures	3	8	
Skin bruises — no. of subjects (%)	27 (4)	63 (10)	<0.001
Cumulative no. of bruises	42	364	<0.001

*The five most frequent categories of serious adverse events and the five most frequent adverse events leading to discontinuation are listed. A serious adverse event was defined as an adverse event that was judged by the investigators to constitute a hazard or a handicap to the subject.

†The causes of death in the placebo group were bronchial carcinoma (3 subjects), sudden cardiac arrest (2), trauma (2), myocardial infarction (1), pulmonary embolism (1), and exacerbation of COPD (1). The causes of death in the budesonide group were bronchial carcinoma (3), myocardial infarction (2), sudden cardiac arrest (1), ruptured aortic aneurysm (1), and gastric carcinoma (1).

180 ml in the placebo group (P=0.05), or 4.3 percent and 5.3 percent of their respective predicted values (P=0.04).[11]

Budesonide had a more beneficial effect in subjects who had smoked less (Fig. 1). Subjects with a history of smoking that was at or below the median of 36 pack-years at enrollment had a decrease in FEV_1 of 190 ml during placebo treatment and of 120 ml during budesonide treatment (P<0.001). The loss of FEV_1 in three years among subjects with more than 36 pack-years of smoking was 160 ml during placebo treatment and 150 ml during budesonide treatment (P=0.57). Analysis of FEV_1 slopes indicated that age, sex, base-line FEV_1, the presence or absence of serum IgE antibodies, and reversibility of airflow limitation had no significant effects on the outcome of treatment.

Similar percentages of subjects stopped smoking in both treatment groups; thus, stopping smoking did not explain the difference in the change in FEV_1 between the groups. When we compared the change in FEV_1 between the subjects who continued smoking at the same rate and those who either decreased their consumption by more than five cigarettes per day or stopped completely, we found a nonsignificant trend toward a beneficial effect in addition to the effect of budesonide.

Side Effects and Safety

More subjects in the budesonide group had skin bruising (Table 3). In total, 10 percent of subjects in the budesonide group and 4 percent of those in the placebo group had bruises during the study (P<0.001). The highest prevalence of bruises at any visit was 4.9 percent in the budesonide group and 1.4 percent in the placebo group.

Bone density was measured in 194 subjects (102 in the budesonide group and 92 in the placebo group). There was no significant change over time and no significant effect of treatment on bone density, except for a small but significant difference at the femoral trochanter in favor of budesonide. The yearly decline in the bone density of the trochanter was 0.38 percent in the placebo group and 0.04 percent in the budesonide group (P=0.02).

Two sets of radiographs of the spine were assessed in 653 subjects, 185 women and 468 men. At randomization, 43 in the budesonide group (13.4 percent) and 38 in the placebo group (11.5 percent) had at least one vertebral fracture. During the study, new fractures were unusual (three in the placebo group and eight in the budesonide group) and were similarly distributed (P=0.50).

Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects and were equally distributed between the groups (data not shown).

Serious Adverse Events

Serious adverse events were equally distributed between the groups (Table 3). Seventy patients in the budesonide group were withdrawn from the study, as compared with 62 in the placebo group ($P=0.51$). More subjects in the budesonide group withdrew from the study because of nonserious adverse events (35, vs. 23 in the placebo group), mainly oropharyngeal candidiasis (8 in the budesonide group and none in the placebo group) and local irritation of the throat or dysphonia (8 in the budesonide group and 2 in the placebo group).

DISCUSSION

Patients with COPD must always be advised and encouraged to stop smoking, and they should be offered treatment programs to facilitate smoking cessation. Nonetheless, some patients continue to smoke. In such patients with mild COPD, we found that the use of inhaled budesonide was associated with a small, one-time improvement in the FEV_1 after bronchodilator use, but that it did not appreciably affect the long-term progressive decline in lung function.

In the placebo group, the postbronchodilator FEV_1 declined by a median of 180 ml over a period of three years, the median slope being −65 ml per year. In the budesonide group, the median decrease in FEV_1 over the three years was 140 ml. The benefit of budesonide was limited to the initial six months of treatment. The beneficial effect of budesonide was greater in subjects with a history of fewer pack-years of smoking.

We studied subjects with mild COPD (mean FEV_1, 77 percent of the predicted value at base line) and a history of moderate-to-heavy cigarette smoking. These characteristics are similar to those of the patients in the Lung Health Study.[1] We attempted to exclude subjects with asthma by eliminating those with a history of asthma or any other atopic disease or with reversible airflow limitation. The presence or absence of IgE antibodies or the degree of reversibility of the airflow limitation did not influence the effect of budesonide. The decline in FEV_1 in the placebo group corresponds with findings in other long-term follow-up studies of COPD.[1,19,20]

Most studies of glucocorticoid treatment in patients with COPD have examined short-term effects on airflow limitation.[8,16,21-29] Results have been variable, but several studies have found an increase in FEV_1 after treatment with oral or inhaled glucocorticoids.[21,22,25,29] The change in FEV_1 during the first months of our study is in line with these findings. Few studies have investigated the effect of glucocorticoid treatment on the long-term change in FEV_1 in patients with COPD. Two retrospective studies suggested that daily treatment with prednisolone might slow the progressive decline in FEV_1.[30,31] In a small group of patients with COPD who had previously been treated with bronchodilators, Dompeling et al.[31,32] observed that daily treatment with 800 μg of beclomethasone was associated with an increase in prebronchodilator FEV_1 during the first 6 months of treatment, followed by a decline during the remaining 18 months of the treatment period. In a two-year controlled study in a small group of patients with COPD, Renkema et al.[16] did not find a significant effect of treatment with budesonide (800 μg twice daily alone or in combination with 5 mg of prednisolone daily) on the decline in FEV_1.

We also examined the side effects of inhaled glucocorticoids in a group of middle-aged smokers. An increased prevalence of skin bruising in patients treated with high doses of inhaled glucocorticoids has been reported in cross-sectional studies.[33,34] In our study, the budesonide group had an overall incidence of skin bruising of 10 percent, as compared with 4 percent in the placebo group, with a maximal prevalence at any time of 4.9 and 1.4 percent, respectively. There was also a higher incidence in the budesonide group of oropharyngeal candidiasis and local irritation of the throat, both well-known side effects of inhaled glucocorticoids. We found no significant effect of budesonide on bone density or the fracture rate, although all subjects were smokers and many of the women were postmenopausal — both of which are well-known risk factors for fracture.

The overall effect of three years of treatment with budesonide on FEV_1 in subjects with mild COPD who continued smoking was quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma. Although the base-line FEV_1 is significantly related to the prognosis of patients with COPD,[20] we cannot extrapolate our findings to assess the potential effect on disability or mortality. The small, overall, one-time beneficial effect on pulmonary function and the possibly more pronounced effect in the subgroup of those who had smoked less must be balanced against the risk of local and systemic side effects.

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APPENDIX

The following physicians enrolled patients in the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease: Belgium — M. DeJonghe, J. Aumann, W. Vincken, and W. DeBacker; Denmark — A. Kok-Jensen, R. Dahl, and P. Tønnesen; Finland — T. Vaita, S. Koskinen, P. Tukiainen, P. Saarelainen, and R. Kulmala; Italy — A. Potena, C. Giuntini, A. Foresi, and S. Bianco; the Netherlands — R. van Altena, F.P. Martsen, L. Greefhorst, and P. van Spiegel; Norway — N. Ringdal, C.A. Stendal, G. Ves, V. Soyset, and G.M. Arckless; Spain — R. Rodriguez Roisin, J. Morera Prat, J.M. Marin Trigo, A.A. Farcia-Navarro, and S.A. Leopoldo; Sweden — B. Lundback, K. Strom, L. Lazer, and T. Mansson; United Kingdom — J. Gibson, A. Wade, P. Ind, and A. Tattersfield. The following committee members were involved in the study: Safety Committee — J. Boe, Norway; T.-B. Conradson, Sweden (Astra Draco); L.M. Fabbri, Italy; and H. Magnussen, Germany. Scientific Committee — A. Tattersfield, United Kingdom; R. Dahl, Denmark; G.J. Huchon, France; B. Mossberg, Sweden; P. Paoletti, Italy; R. Rodriguez Roisin, Spain; and J.C. Yernault, Belgium. The following consultants were involved in the study: P. Quanjer and P. Sterk (spirometry), the Netherlands; J.M. Vonk (statistics), the

Netherlands; and O. Johnell (evaluation of radiographs and dual-energy x-ray absorptiometric measurements), Sweden. The following Astra employees were involved in the study: G. Jönsson (study coordinator), H. Hansson (data entry), M. Broddene (safety evaluation), and H. Holm (bioanalysis). The national medical monitors were C. Wouters, A. Vandenbossche, M. Vilstrup, C. Olsen, T. Svahn, E.-L. Kiiskilä, C.M. Morelli, M. Schiassi, E. Tammeling, M. van den Dobbelsteen, V. van Driel-Schrooten, S. Holthe, R. Estiarte Navarro, E. Pellicer Thoma, A. MacLean, F. Gien, and E. Story.

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 Item 6. Exhibit D

COMMENTARY

Inhaled steroids in COPD

See page 773

Chronic obstructive pulmonary disease (COPD) is a huge health problem in terms of mortality and morbidity. In the UK, in the 3-year period 1990–92 the numbers of deaths attributable to COPD were 51 500 for men over 65 and 30 000 for women over 65.[1] These numbers far exceed the 1500 to 2000 deaths per year from asthma in the UK. In terms of hospital admissions for adults, COPD is a much greater burden on the health service than is asthma.

Over the past 10 years there has been a substantial change in the management of asthma, with the introduction of management guidelines and their emphasis on the use of inhaled corticosteroids in all patients except those with mild asthma.[2] These recommendations are firmly backed by data from many clinical trials.

Inhaled steroids improve pulmonary function and symptoms in asthma, enhance quality of life, prevent allergen-induced bronchoconstriction in atopic patients and, when used chronically, increase exercise capacity. An emphasis in recent trials has been on the ability of inhaled corticosteroids to prevent exacerbations or worsening of asthma,[3] and it is this effect that accounts for the ability of these agents to prevent hospital admissions and for the increasing circumstantial evidence that inhaled corticosteroids decrease the asthma death rate.[4,5]

This clinical-trial evidence is supported by research into the effects of inhaled corticosteroids on the pathology of asthma. Airways inflammation in asthma is characterised by an increase in CD4-lymphocyte count, an increase in eosinophil count, a small increase in mast-cell count, thickening of the basement membrane, and disruption of the airway epithelium. Inhaled steroids cause a decrease in the number and state of activation of CD4 cells, eosinophils, and mast cells and restitution of the normal airway epithelium.[6] There is less evidence that they reverse subepithelial fibrosis.

The evidence that inhaled corticosteroids are of benefit in COPD, either clinically or pathophysiologically, is scanty, yet these agents are widely used in the management of this disorder. This discrepancy is partly due to the inevitable diagnostic confusion between asthma in the elderly and COPD. Another reason is that, faced with a patient for whom few other treatments are of clear-cut benefit, physicians will try a treatment they judge to be safe, even if the likelihood of benefit is low. A third reason is that during acute exacerbations of COPD systemic steroids may speed recovery, an effect that is taken as evidence that steroids will be of help in that individual in the long term.

In recently published guidelines[7] on the management of COPD, inhaled corticosteroids are recommended only for those patients who show a clear objective response to a formal trial of either oral or high-dose inhaled steroids. For an unselected group of patients with COPD, a positive trial of steroids is defined as a 15% increase in baseline FEV_1, with an absolute increase of greater than 200 mL. A change of this magnitude is seen in 10–15% of patients with COPD.

COPD is a clinical descriptive term for patients, mostly elderly, who have airflow obstruction that is not relieved completely with therapy. It is caused by at least three distinct pathological processes, which may occur separately or, in many patients, concurrently. These processes are destruction of alveolar walls causing emphysema, chronic bronchitis with hypersecretion of mucus, and chronic asthma.[8] There are few studies on the airway pathology of COPD, but the pathological features are distinct from those of asthma. In COPD there is a predominance of CD8 cells, an increase in number of neutrophils, no thickening of the basement membrane, and no evidence of disruption of the airway epithelium, but there is an increase in squamous metaplasia.

It is commonly thought that the 15% of patients who respond to steroids represent a group with a substantial chronic asthmatic component. This view is supported by a study[9] that showed that in patients with a clinical diagnosis of COPD, those with biopsy features of asthma (high number of eosinophils and thickening of the basement membrane) were the ones who improved with high-dose prednisolone over 2 weeks. The limited number of studies of the effect of steroids on airways inflammation in COPD has shown little evidence of an acute anti-inflammatory effect,[10] although there may be some effect on airway protein leakage.[11] Taken together the evidence supports the recommendation in the COPD guidelines that patients who show a definite response to steroids (presumed to be those with a component of asthma to their disease) should be treated with inhaled corticosteroids. The unanswered question is how to deal with the remaining 80–90% of patients who do not show a clear-cut response to steroids. This group of patients will not have much improvement in pulmonary function with corticosteroids, so other outcome measures must be used.

Survival in COPD correlates inversely with FEV_1, and

any treatment that slows the accelerated decline in FEV_1 in COPD will be likely to reduce mortality. One question that is the subject of at least two large-scale studies is whether inhaled corticosteroids slow the decline of FEV_1 in patients with COPD. The EUROSCOP study is investigating this issue in mild COPD.[12] Initial results suggest that any effect is small and transitory. The ISOLDE study is investigating the question in a group of patients with more severe COPD.[13] In shorter-term trials it would be sensible to look at outcome measures such as prevention of exacerbations of COPD (which are a common and important clinical problem), exercise capacity, and quality of life.

The study reported in today's *Lancet* is a comparison of the effects of high-dose inhaled steroids (fluticasone 500 μg twice daily) with placebo over a 6-month treatment period. The primary outcome variable was the exacerbation rate, with secondary outcome variables being symptoms, pulmonary function, 6 min walking distance, and breathlessness. The overall rate of COPD exacerbations was lower than had been predicted from pilot studies, and no significant difference was seen between the groups. However, there seemed to be a shift in severity of exacerbations, with fewer patients in the active-treatment group having severe exacerbations. This possible effect of inhaled steroids in COPD needs to be investigated. There was also a small but clinically and statistically significant improvement in peak expiratory flow rate of 15 L/min in the inhaled-steroid group, and this finding was supported by small improvements in spirometry, symptoms, and walking distance. The individuals recruited had moderately impaired pulmonary function, with less than 8% reversibility in FEV_1 after bronchodilator and no evidence of blood eosinophilia, which might indicate asthma. The only predictor of response that the investigators found was a duration of COPD of greater than 10 years. This earlier onset of symptoms among responders could be interpreted as being due to the contribution of a component of asthma to their airflow obstruction.

The study did not investigate lower doses of inhaled steroids, which may also be effective. There is no indication from the data of a loss of activity over 6 months, but further studies looking at the duration of any effect are needed.

What lessons for clinical practice and research can be drawn from this study? There should be no change in the recommendation in the COPD guidelines that patients who show striking response to oral or inhaled corticosteroid should be treated with inhaled steroids. The study shows that a small absolute improvement in pulmonary function is associated with clinical benefit in terms of symptoms, exercise capacity, and possible severity of exacerbations. If that is so, a reasonable approach would be to lower the threshold for concluding that a patient's illness has undergone a clinically important improvement with inhaled steroids. If after several months of treatment with high-dose inhaled steroids, peak flow improves by 15 L/min or more and the severity and the number of exacerbations fall, the patient should continue on inhaled steroids. If these variables do not improve, there is no compelling reason to continue with inhaled steroids. Since it is difficult to demonstrate clinical predictors of response, an area that may justify further investigation is whether pathological appearances—especially eosinophils or thickened basement membrane—should be used to predict a response.

The broader implication of this study is that the current treatment of COPD remains extremely unsatisfactory. Obviously, avoidance or cessation of smoking is the key to improving the outlook for patients with COPD. However, even if patients succeed in giving up smoking, there will still be many symptomatic patients for the forseeable future. It is vital that understanding of the basic mechanisms in COPD improves. Present evidence suggests that inflammation present in COPD is poorly responsive to steroids or that, unlike asthma, this airways inflammation is not the primary problem in the disease. New treatments for COPD are urgently required.[14]

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Ankylosing spondylitis, HLA B27, and beyond

Publication of the landmark *Lancet* paper showing the strong association between HLA B27 and ankylosing spondylitis 25 years ago[1] stimulated an avalanche of research into HLA/disease associations. The subsequent weaker associations of HLA B27 with anterior uveitis, reactive arthritis, sacroiliitis, late-onset pauciarticular juvenile chronic arthritis in boys, and inflammatory bowel disease with axial joint involvement suggested a common genetic determinant for a group of disorders already linked as seronegative spondyloarthropathies by the clinical observations and family studies of the late Verna Wright,[2] and others. Because reactive arthritis can

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Item 6. Exhibit E

To C 9/n -07

MEETING REPORT

Highlights of a symposium on chronic obstructive pulmonary disease held at the National Heart and Lung Institute, London, July 7–8, 1998.

COPD: New Developments and Therapeutic Opportunities

by Peter Norman

Summary

The deficiencies of current therapies and the potential benefits of novel approaches to chronic obstructive pulmonary disease (COPD) were reviewed at a symposium organized at the National Heart and Lung Institute, London, U.K., July 7–8, 1999. Several speakers discussed different facets of the disease. The keynote lecture dealt with two major, but distinct themes: the utility of computerized tomographic scanning as both a quantitative and a qualitative tool and the recent observation that retinoic acid could produce new alveolar growth, emanating from ducts, in hamsters when it was administered after instillation of elastase. Regarding current therapeutic approaches, bronchodilators are the mainstay of existing therapy, while the use of mucolytics varies markedly between countries. The role of steroids in the treatment of COPD is confused. There is surprisingly little evidence of any clinical benefit from the use of antibiotics. Potential future therapies include M_3-selective muscarinic antagonists, chemotactic mediators, protease inhibitors and antiinflammatory agents.

A fascinating meeting on chronic obstructive pulmonary disease (COPD) was arranged by Profs. Peter Barnes and Neil Pride, of the National Heart and Lung Institute, London, U.K. (NHLI), to highlight the growing significance of COPD, to emphasize the paucity of our knowledge of the disease mechanisms and to address the problems of treating the disease. To this end, the deficiencies of current therapies and potential novel approaches were discussed.

The disease

Peter Barnes gave the introductory lecture. COPD is a disease characterized by irreversible airways obstruction and encompasses both chronic bronchitis and emphysema. It has a major economic impact, being responsible for 10–15% of sickness benefit in the developed world. It is responsible for 25% of deaths in the United States, and the WHO is currently predicting that it will be the third major cause of death in the world within 20 years.

Prof. Barnes was the first of several speakers to show a slide based on the work of Fletcher and Peto illustrating the progressive decline of forced expiratory volume (FEV_1), a measure of lung function, with age, by 25 ml annually in normal subjects. This is substantially accentuated by smoking, albeit in only a proportion of smokers, and this progressive decline in lung function eventually results in death. Smoking cessation results in a slowing, but not a reversal, of this deterioration.

John Britton (Nottingham University, U.K.) considered the disease's epidemiology. Currently it is substantially more prevalent in men than women, but this is attributed to the historically lower prevalence of smoking in women. Changes in smoking patterns suggest such differences will soon disappear. Smoking is the primary risk factor (83%), although both passive smoking and heavy exposure to dust, for example, in coal miners, are additional risk factors. These risk factors result in COPD being a disease of late middle and old age,

occurring only rarely in the under-45 population.

There are pronounced geographical differences in the incidence of COPD. It is most common in Northern and Eastern Europe with progressively lower frequencies in the United States, Mediterranean Europe and Japan. While such differences may be partially explicable due to differences in diagnosis, there are presumed to be genetic factors also involved. Currently the only known contributory factor is α_1-antiprotease deficiency.

Different facets of the disease were reviewed by Peter Jeffrey, Terry Tetley, Duncan Rogers (all NHLI) and Rob Stockley (Queen Elizabeth Hospital, Birmingham, U.K.), while Trevor Hansel (NHLI) highlighted the problems of designing appropriate clinical trials. These ideally require the identification of relevant surrogate markers and better-defined endpoints than small changes in the rate of decline of FEV_1 for the long (two- to three-year) phase III studies.

Although it can be difficult to distinguish between asthma and COPD on the basis of lung function measurements, there are major differences in the lung pathology. Bronchitis is characterized by damaged cilia, goblet cell hyperplasia and mucus hypersecretion with stenosed small airways but comparatively little epithelial damage. In emphysema, there is substantial inflammation of the peripheral airways accompanied by significant acinar damage. In both conditions there is extensive infiltration by CD8+ lymphocytes, with a ninefold elevation of lung macrophages and a 100-fold increase in neutrophil levels, predominantly within the epithelium.

Associated with this elevation of neutrophils are significant increases in interleukin-8 (IL-8) levels and an increase in proteolytic enzymes, principally neutrophil elastase but also matrix metalloproteases (MMPs). A key, unanswered, question is which factors are predictive of a predisposition to COPD. Thus, studies examining cell markers in smokers should only see pronounced changes in a fraction (10–20%) of the patients examined. IL-8 chemotactic activity in sputum from smokers falls into this category, whereas levels of a number of proteolytic enzymes (cathepsin L, collagenase and gelatinase B) are generally elevated in all smokers. There are also some data suggesting that the cytokines IL-1 and tumor necrosis factor-α are involved in the disease pathogenesis.

Excessive mucus secretion is a symptom of the disease, but does not appear to be a causal factor. The presence of excessive mucus allows bacterial colonization, facilitating exacerbations, in addition to obstructing the airways. Once the disease is established, both mucus hypersecretion and mucous cell hyperplasia are observed. While mucolytic agents have the potential to improve mucus clearance, truly effective agents are not available. Two mucin genes, MUC5A and MUC5B, appear to be of major significance in the airways, but their regulation is not yet understood.

The keynote lecture was presented by James Hogg (Vancouver, Canada) and dealt with two major, but distinct themes. He first addressed the utility of computerized tomographic scanning both as a quantitative tool to evaluate the progression of the disease and, more qualitatively, to facilitate identification of nonfunctioning areas of the lung that might be removed in lung volume resection surgery.

Until recently there has been no evidence that therapeutic intervention might be able to reverse, rather than halt, the destruction of lung tissue. The second part of Dr. Hogg's talk addressed the recent observation by Donald and Gloria Massaro that retinoic acid could produce new alveolar growth, emanating from ducts, in hamsters when it was administered after instillation of elastase. Precise measurements are required to observe functional changes in this model.

Dr. Hogg suggested that the changes in the ratio of lung surface to volume mirror those observed early in clinical emphysema. Identifying the critical transcriptional mechanisms involved will undoubtedly become a major research effort, given the significance of the observations by the Massaros. However, he did suggest that it would be desirable to repeat such observations in an animal where alveolar growth stops at birth, such as the guinea pig, which would better model the human condition, where growth stops at four years of age.

Current therapy

An overview of current therapeutic approaches to the treatment of COPD was provided by Philip Ind (NHLI), while Peter Calverley (University Hospital, Liverpool, U.K.) considered alternatives to pharmacological intervention. Neil Pride (NHLI) reviewed the evidence from recent long-term clinical studies with inhaled steroids and Robert Wilson (NHLI) addressed the role of antibiotics in the treatment of exacerbations.

Bronchodilators provide the mainstay of existing therapy, and both inhaled muscarinic antagonists (generally ipratropium bromide) and β_2-agonists are routinely employed. The effects of members of these two classes are additive, and they are now often administered as a combination preparation. A more recent alternative is the use of q.i.d. ipratropium plus a long-acting β_2-agonist. While theophylline has beneficial effects, its use in elderly patients is often constrained by side effects.

The use of mucolytics varies markedly between countries. Because of their questionable efficacy, the availability of these drugs is often restricted by regulatory authorities. However, there is some evidence substantiating the efficacy of *N*-acetylcysteine.

The role of steroids in the treatment of COPD is confused. It has been commonly held that they are ineffec-

tive, but they are commonly prescribed by general practitioners. Inhaled formulations are designed for the treatment of asthma, so they do not deliver significant doses of steroids to peripheral lung. Few studies have addressed the role of systemic steroids in treating acute exacerbations, but administration of oral prednisolone for two weeks appears to improve lung function.

Ongoing studies such as EURO-SCOP and ISOLDE have examined the efficacy of three years' treatment with inhaled **budesonide**. The available results suggest that the benefit is relatively small, but significant improvements in FEV_1 were noted in the first three months of treatment. **Fluticasone** treatment has also been shown to result in (small) improvements in FEV_1 over a six-month period.

While antibiotics are commonly administered to patients suffering from COPD exacerbations, there is surprisingly little evidence of any clinical benefit from their use. Unless there is bacterial colonization of the lung, by organisms such as *Haemophilus influenzae*, even placebo treatment is effective in over 50% of cases. However, diagnosis of infection requires correct diagnosis from the presence of purulent sputum or, preferably, by culturing bronchial brushings.

There has been a dramatic increase in antibiotic resistance of the common infectious organisms, especially in the United States. There nearly all infections with *Moraxella catarrahlis* are resistant, with 50% of *H. influenzae* resistant and also with high β-lactamase activity, and 24% of *Streptococcus pneumonia* infections are also resistant. Significant resistance to quinolones has not yet been observed, but it was stressed that indiscriminant use of the new quinolones could lead to substantial problems in treating such cases. New guidelines, currently being agreed, will recommend the use of **ciprofloxacin**, **azithromycin** or **amoxicillin + clavulanic acid** for the treatment of chronic purulent infections.

The more severe COPD patients are commonly underweight, and it was suggested that this worsens the disease prognosis. Oxygen treatment is beneficial in improving life expectancy in severe patients, but only when they are significantly hypoxemic (PaO_2 < 7.3 kPa). A recently developed radical alternative for emphysema patients is lung volume reduction surgery. If performed carefully, this appears to be at least as effective as a single lung transplant. While a double lung transplant affords improved lung function, it does not improve the disease mortality, in contrast to what occurs in patients with cystic fibrosis.

Potential therapies

Muscarinic antagonists

The identification of distinct muscarinic receptor subtypes and the comprehension of their physiological role has led to the realization that it is less desirable to block the M_2 receptor in treating COPD. Peter Barnes indicated that these act as autoreceptors, and hence blockade of these would tend to counteract the benefits gained by blocking M_3 receptors.

Both Pfizer and Boehringer Ingelheim have developed new selective muscarinic antagonists, but with very different properties. Pfizer has identified both a selective M_3 antagonist, **darifenacin** (Fig. 1), and an M_1/M_3-selective antagonist, **revatropate** (Fig. 1). Both were stated to be short-acting drugs, like ipratropium bromide, and clinical results with revatropate have proved disappointing.

Tiotropium bromide (Boehringer Ingelheim; Fig. 1) has no intrinsic muscarinic receptor selectivity, displaying subnanomolar K_D values at all three receptor subtypes, but has the unusual property of kinetic selectivity with a dissociation half-life of 34.7 hours from M_3 receptors compared to 3.6 hours from M_2 receptors. This drug behaves as a long-acting and selective antagonist both *in vitro* and in animal studies. In humans, it is well tolerated when administered as a dry powder and produces a dose-related bronchodilatation which lasts for over 24 hours. A four-week phase III study in COPD patients has confirmed the efficacy, and tolerability, of once-daily dosing, with drug effects persisting for a week after cessation of treatment. This drug is rapidly metabolized when swallowed, so side effects are minimal. Peter Barnes stated that oral administration of selective M_3 antagonists produces all the undesirable side effects such as dry mouth. He also indicated that the old muscarinic antagonist **glycopyrronium bromide** (A.H. Robins; Fig. 1) behaves in a similar manner to tiotropium and is now being developed for the treatment of COPD.

Chemotactic mediators

Sputum from COPD patients is highly chemotactic for neutrophils. This is principally due to the presence of high concentrations of the chemokine IL-8 and the eicosanoid leukotriene B_4 (LTB_4), with each accounting for about 40% of the chemotactic activity in sputum. LTB_4 levels are substantially elevated in asymptomatic smokers, and the decline of lung function has been shown to correlate to the neutrophil concentration in sputum.

The effects of LTB_4 could be reduced either via inhibiting its synthesis with lipoxygenase inhibitors or with specific BLT receptor antagonists. Although many lipoxygenase inhibitors have been developed for the treatment of asthma, with Abbott's zileuton approved for that indication, there are no reports of their clinical evaluation in COPD. A number of BLT antagonists are currently in clinical development for the treatment of psoriasis (VML-295, Lilly, Vanguard Medica; ONO-4057, Ono) or arthritis (CGS-25019C; Novartis), with no efficacy seen in studies in asthmatics with, for example, LY-293111 (Lilly).

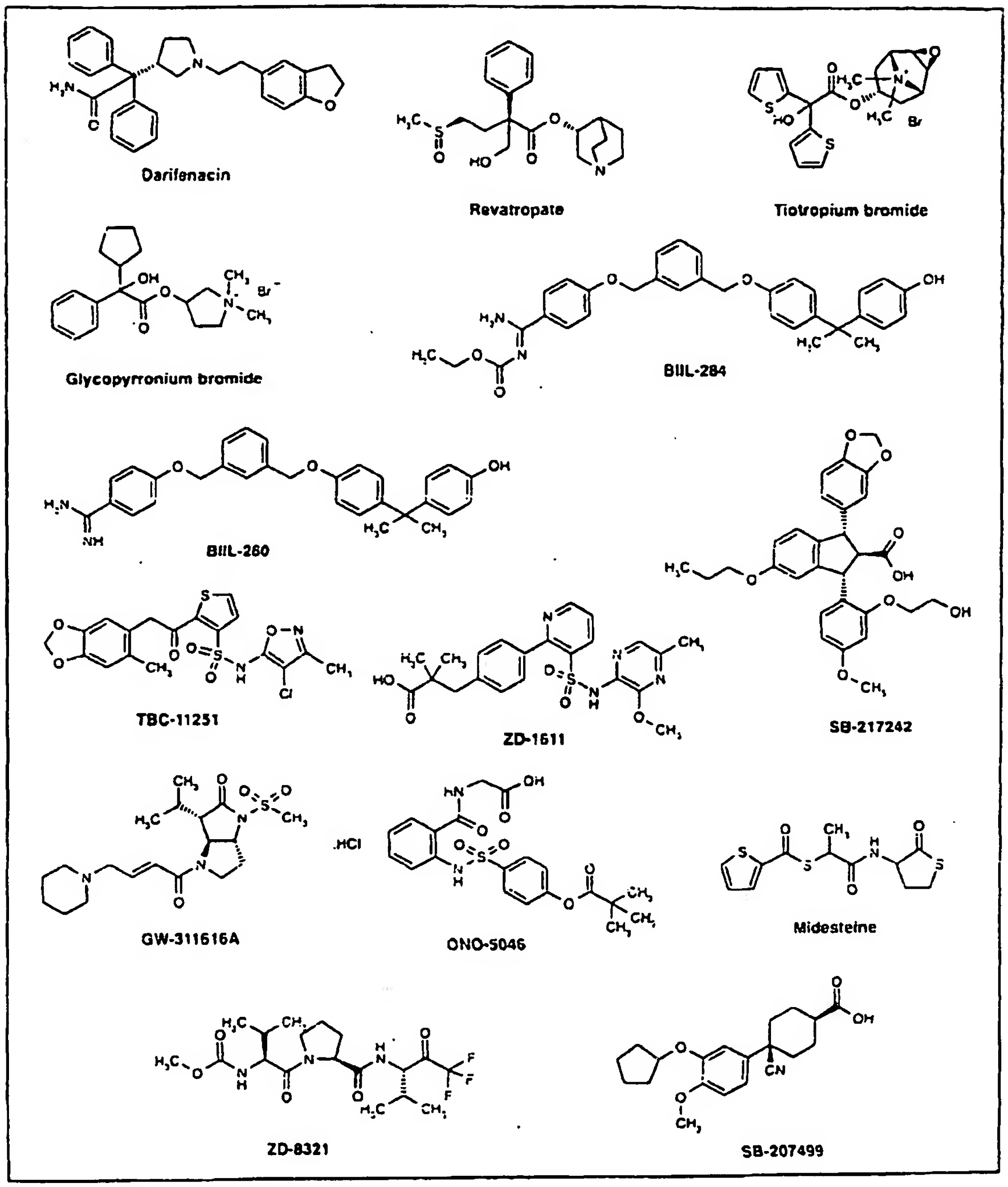

Fig. 1. Structures of compounds discussed at the symposium.

Boehringer Ingelheim has developed a novel antagonist, the phenylguanidine derivative BIIL-284 (Fig. 1), and has just initiated phase I studies with the intention of developing this drug for the treatment of COPD. Franz Birke (Ingelheim) described the pharmacological profile of this long-acting compound. BIIL-284 is a formate ester prodrug, which is cleaved *in vivo* to the more active free guanidine **BIIL-260** (Fig. 1).

TABLE I: ACTIVITY OF SELECTED BLT RECEPTOR ANTAGONISTS

DRUG	K_i (nM) [^{3}H]-LTB_4 BINDING TO HUMAN NEUTROPHILS	ED_{50} (mg/kg po) LTB_4-INDUCED MOUSE EAR INFLAMMATION	ED_{50} (mg/kg po) LTB_4-INDUCED NEUTROPENIA IN MONKEYS	$t_{1/2}$ (hours) LTB_4-INDUCED NEUTROPENIA IN MONKEYS
BIIL-284	150	0.008	0.004	24
BIIL-260	1.3	–	–	–
CGS-25019C	0.9	5.5	2.5	1.0
LY-293111 (VML-295)	24	>20	3.1	3.0

Dr. Birke presented data comparing these compounds with two other antagonists (Table I). In studies in primates, administration of **BIIL-284** resulted in a greater than 95% inhibition of Mac-1 expression on circulating neutrophils, and a 1-mg/kg oral dose resulted in a greater than 90% inhibition of LTB_4-induced neutropenia 24 hours after dosing. Toxicological studies have failed to show any adverse effects of this drug.

IL-8 is a CXC chemokine acting on both CXCR1 and CXCR2 receptors. These G-protein–coupled receptors, sometimes referred to as IL-8 receptors, are also activated by other chemokines (CXCR1 by GCP-2 and CXCR2 by Gro, NAP-2 and ENA-78), and are heavily expressed on neutrophils but only lightly expressed on eosinophils.

Amanda Proudfoot (Serono, Geneva) reviewed this area and indicated that interferon gamma selectively up-regulates CCR receptors, but not CXCR receptors, on human neutrophils. She and her colleagues have found that chemokines are selectively recognized by glycosaminoglycans. These selectively recognize IL-8 in the following order: heparin > heparan sulfate > chondroitin sulfate; such interactions were suggested to provide a mechanism for localized *in vivo* control of chemokine effects.

Both CXC and CC chemokine antagonists are known that have been produced by modification of the N-terminus. The CCR antagonist Met-RANTES has been used to demonstrate an involvement of CC chemokines in models of asthma and arthritis. No data on IL-8 antagonists, either peptide analogues or small-molecule nonpeptides, were presented.

There is also a significant body of evidence that implicates the peptide endothelin-1 as playing a pathological role in COPD and especially in pulmonary hypertension. Tony Rebuck (SmithKline Beecham, U.S.A.) reviewed the therapeutic potential of endothelin (ET) antagonists. There is currently no evidence to indicate an elevation in ET levels in the lungs of COPD patients, whereas levels are elevated in patients with chronic hypoxia.

Endothelin antagonists are effective in animal models of hypoxia. The nonselective antagonist **SB-217242** (SmithKline Beecham; Fig. 1), at 3.6 mg/day, prevented hypoxia-induced increases in pulmonary artery pressure in a rat model of chronic hypoxia. This compound, like **TBC-11251** (Texas Biotechnology; Fig. 1) and **ZD-1611** (Zeneca; Fig. 1), is currently in phase II studies for the treatment of pulmonary hypertension, but is also under clinical evaluation for the treatment of COPD. Such studies should help clarify the role of endothelin in lung diseases provided appropriate clinical endpoints are defined.

Protease inhibitors

Activated neutrophils also release high levels of the serine protease elastase. When the normal physiological control mechanisms are defective, this enzyme causes substantial degradation of the extracellular matrix, leading to extensive alveolar damage and eventually resulting in emphysema. Therapeutic approaches to elastase inhibition were discussed by Robin Smith (Glaxo Wellcome, Stevenage, U.K.). He described the activities of three inhibitors but did not reveal their structures.

Both polypeptide and small-molecule inhibitors have been sought, with much of this effort directed toward the latter. Although both purified and recombinant forms of the natural inhibitor (**α_1-antitrypsin**) are available, effective inhibition requires gram quantities in the lung, thus limiting its utility on cost grounds. Aerosol formulations of the smaller peptide SLPI (**secretory leukocyte protease inhibitor**) are under development by both Synergen and Teijin in full-length and C-truncated forms, respectively, but clinical results were not discussed.

Because elastase is stored in an active form in azurophil granules within the neutrophil, at a concentration of 5 mM, synthetic inhibitors have been targeted at both extracellular and intracellular elastase. **GW-311616A** (Glaxo Wellcome; Fig. 1) is a low-molecular-weight inhibitor of intracellular elastase. This compound, in preclinical development, is based on a novel template and is orally active in dogs at doses of 0.2–2 mg/kg. It was implied to be more potent *in vivo* than DMP-777 and said to be a slowly reversible inhibitor.

ONO-5046 (Ono), **midesteine** (Medea Research) and **ZD-8321** (Zeneca) (Fig. 1) are all extracellular inhibitors currently reported to be in phase II or III studies for the treatment of emphysema. Midesteine is a weak enzyme inhibitor (K_i = 1.4 μM) that is well tolerated in humans but displayed limited efficacy in a four-week study in COPD patients. Glaxo had earlier been investigating compounds with such activity, and both **GR-243216** and **GR-243214** were described as active, at 3 μg intratracheally, in hamster models of emphysema. GR-243216 was the more potent compound, with a K_i value of 6 nM and a 16-hour duration of action.

David Lomas (Cambridge University, U.K.) described studies on the mechanistic defects in Z α_1-antitrypsin. This point mutation results in the breaking of an intramolecular salt bridge, and allows the mutant α_1-antitrypsin to polymerize, in a temperature-dependent manner, rather than inactivate elastase. The resulting protease-antiprotease imbalance results in the genetic form of emphysema. His group's progress in defining the mechanisms involved and delineating the structure of the active site offers new possibilities for rational drug design to prevent the problems that arise from this relatively common genetic disease, which accounts for 1–2% of all cases of emphysema.

Recent studies have shown the lungs of emphysema patients to contain elevated levels of the MMP enzymes gelatinase B and collagenase. These are secreted both from airway epithelium and alveolar macrophages. It remains unclear whether they play a causal role in the disease pathogenesis. Their elevation may result from inactivation of tissue inhibitors of metalloproteases (TIMP). It has been suggested that collagenase activity in lavage fluid may be a better marker for the diagnosis of emphysema than elastase activity. Such observations suggest that MMP inhibitors may have a role to play in the treatment of COPD.

Antiinflammatory agents

Three possible approaches to the reduction of inflammation were discussed. The use of novel antioxidants to attenuate the damage caused by cigarette smoke was discussed by Bill MacNee (Royal Infirmary, Edinburgh, U.K.), the role of adhesion molecules by Paul Hellewell (Sheffield University, U.K.) and inhibition of phosphodiesterase IV (PDE IV) by Mark Giembycz (NHLI).

While integrins are heavily involved in leukocyte recruitment and trafficking in inflammatory diseases, there is currently relatively little evidence to substantiate a role for these carbohydrates in COPD. The small size of pulmonary alveolar capillaries (5–7 µm in diameter) precludes neutrophil rolling, since the cells need to deform to fit into the capillaries. It is currently believed that their sequestration is an integrin-independent mechanism. In addition, interfering with the effects of β_2-integrins might compromise host defense mechanisms, as seen in patients with leukocyte adhesion deficiency.

While oxidants normally cause damage via inactivation of regulatory enzymes, the healthy lung contains high concentrations of several antioxidants in epithelial lining fluid. These provide some protection, but depletion of some antioxidants is observed in chronic smokers. Glutathione (GSH) appears to the most significant of these undergoing initial depletion, followed by a rebound increase due to increased transcriptional regulation of gamma-glutamylcysteine synthetase. It was suggested that these effects might be mediated via tumor necrosis factor.

Vitamin E supplementation has only modest effects *in vivo*, although it is effective *in vitro*. More promising therapeutic approaches appear to be the administration of exogenous superoxide dismutase or catalase or the identification of agents which up-regulate GSH. *N*-Acetylcysteine, an antioxidant available in some markets, can up-regulate GSH, but only slowly and at unacceptably high oral doses. The development of *N*-isobutyl-L-cysteine as an inhaled formulation may prove more effective in this regard.

The use of PDE inhibitors, particularly selective PDE IV inhibitors, offers the opportunity of preventing the activation of inflammatory cells, and thus the release of superoxide, LTB_4, IL-8 and elastase. Macrophages, neutrophils and eosinophils all contain several isoforms of PDE IV, albeit in varying ratios. PDE IV inhibitors also inhibit the activation of monocytes and epithelial cells.

Clinical evidence to substantiate a therapeutic role for PDE IV inhibition in COPD is currently confined to limited data obtained with theophylline. Theophylline treatment for four weeks, at a dose producing a plasma concentration of 9.2 µg/ml, reduced the neutrophil count, myeloperoxidase and lactoferrin levels in induced sputum. However, it may not have been acting via inhibition of PDE IV.

No other clinical data are currently available, as, until recently, PDE IV inhibitors were only being developed for the treatment of asthma and arthritis. Nevertheless, *Ariflo* (SB-207499; SmithKline Beecham; Fig. 1), a selective PDE IV inhibitor, is now being developed for both indications. Although, in common with most PDE IV inhibitors, this compound induces emesis, it has satisfactorily completed a four-week phase II study in COPD patients. Patients are currently being recruited for a phase III study. It was stated that the phase II study resulted in a significant improvement in FEV_1 and other (unspecified) parameters.

Antismoking therapy

Given the primary causal link between COPD and smoking, it would have been inappropriate not to discuss the subject of antismoking therapy. Martin Jarvis (University College Medical School, London, U.K.) described how pharmacological intervention is the only effective controlled approach. Nicotine replacement therapy has proved effective initially in the form of chewing gum and more recently as nasal sprays, inhalers or transdermal patches. The more recent methods are more effective than gum, but there are still difficulties in continued cessation and smoke of these therapies result in a transferred nicotine dependence.

Alternative approaches are now being investigated. Trials with the α_2-agonist clonidine produced efficacy comparable to that of nicotine gum, but an unacceptable level of side effects. Concurrent administration of the nicotinic antagonist mecamylamine with the use of nicotine patches is producing promising results. A sustained-release form of the antide-

pressant bupropion has been developed by Glaxo Wellcome and launched in the United States as *Zyban*. This has been found to be superior to the nicotine patch, although in combination they are more effective. It is unclear by what mechanism bupropion is acting to produce these effects.

Concluding remarks

This well-organized meeting provided a good overview of COPD and highlighted our current lack of understanding of the causal mechanisms involved. While smoking is the primary cause, little evidence was presented to suggest what determines whether smokers will subsequently suffer from COPD.

This lack of understanding has doubtless contributed to the pharmaceutical industry's historical neglect of this major disease. However, there now appears to be a significant awareness of the disease and it has now become a major disease target for a number of companies, evidenced by the large contingents of delegates present from several companies.

It was made clear that existing therapies provide modest therapeutic benefits and that both steroids and antibiotics are commonly used, although their efficacy is highly questionable. Few new therapies are in advanced development, but the long-acting tiotropium bromide will facilitate patient compliance. Clinical studies with the long-acting and highly potent BLT receptor antagonist BIIL-284 should clearly establish the significance of LTB_4 in the disease process. In addition, the emergence of clinical data with the PDE IV inhibitor SB-207499 should improve our understanding of the disease process and help to improve the design of future clinical studies.

There is likely to be an explosion of our knowledge of the pathophysiology of COPD over the next few years. Future meetings on this topic will then point to a more optimistic prognosis for COPD patients.

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ARIAD UPDATES STOCKHOLDERS

In a letter to stockholders dated August 14, 1998, Ariad Pharmaceuticals, Inc. provided an update on the company's progress over the past six months.

In the company's signal transduction inhibitor program, Ariad is developing AP-22408, its lead compound that was created using structure-based drug design. AP-22408 was designed to directly block Src, an intracellular protein that Ariad believes is critical to disease progression in osteoporosis. The compound binds to Src with low nanomolar potency, and has demonstrated highly significant evidence of efficacy in a broadly accepted animal model of osteoporosis. Ariad believes that AP-22408 meets the requirements of the second milestone in its strategic partnership for osteoporosis with Hoechst Marion Roussel (HMR).

In addition, the company expects that products based on *ARGENT*™ (Ariad's Regulated Gene ExpressioN Technology), a proprietary technology designed to allow control of cellular activities through the administration of small-molecule drugs, will be the first to enter clinical testing. AP-1903, the first *ARGENT* drug, is currently undergoing preclinical toxicology and pharmacology studies. Initial clinical trials of AP-1903 are being designed to evaluate the safety of the compound when used with *ARGENT* gene components to treat graft-vs.-host disease in allogeneic bone marrow transplant patients. AP-1903 is expected to enter the clinic before the end of the year.

ARGENT is also being developed as a means to produce orally active therapeutic proteins. In a recent study conducted by Ariad and its joint venture partner Genovo, monkeys received an intramuscular injection of the genetic components of *ARGENT* and the gene for erythropoietin (EPO). After the genetic material was injected into the muscle of the animals, they received a single dose of a small-molecule dimerizer drug. Upon drug administration, the monkeys' muscle cells began producing therapeutically relevant levels of EPO, which continued over time. Ariad is currently engaged in further *in vivo* studies, manufacturing scale-up and preclinical testing of the *ARGENT* orally active therapeutic protein product. The company plans to begin human clinical trials in this program in the first half of next year.

Also during the first half of the year—in March—, the Hoechst-Ariad Genomics Center, a joint venture with HMR to identify therapeutic proteins and novel drug targets for small-molecule drug development, reached its first anniversary. The Genomics Center also established its first research collaboration, in July. Ariad scientists are working with the Center for Prevention of Cardiovascular Disease at the Harvard School of Public Health to identify novel genes involved in cardiovascular disease and cancer.

Item 7

Attorney's Docket No.: 06275-150003 / D 1841-3P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Carl-Axel Bauer et al.	Art Unit	: 1617
Serial No.	: 10/010,283	Examiner	: Jennifer Kim
Filed	: November 13, 2001		
Title	: NEW USE FOR BUDESONIDE AND FORMOTEROL		

BOX AF
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF CHRISTER HULTQUIST, M.D.

I, Christer Hultquist, M.D., declare as follows:

1. I am a physician with a Specialty in Pediatrics (1981) and in Pediatric Allergology (1982). From 1981 to 1991 I was Senior Registrar at the Pediatric unit at the University Hospital in Lund, Sweden, attending children with cystic fibrosis, asthma and related allergic disorders. Since 1991 I have been a Medical Advisor at Astra AB (now AstraZeneca AB), and at present I am serving as the Clinical Development Medical Director for Symbicort® asthma medication (an inhalable medication containing a combination of budesonide and formoterol) at AstraZeneca AB.

2. I was involved in conducting a placebo-controlled 12 month clinical trial that was recently performed using a combination of budesonide/formoterol (under the product name Symbicort®) in the treatment of moderate to severe COPD. 1022 patients were treated in a 2 week initial period with oral prednisolone (30 mg once daily) and formoterol (2 x 4.5 µg twice daily). The patients had the following profile:

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December 13, 2002
Date of Deposit

Julia Doherty
Signature

Julia Doherty
Typed or Printed Name of Person Signing Certificate

Age $\geq$ 40 years

COPD patient for at least 2 years

At least 10 pack years smoking history[1]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/formoterol combination (Symbicort® inhaler) at a dosage of 2 puffs, each puff containing 160 µg budesonide/4.5 µg formoterol, twice per day

Group 2: Budesonide alone (2 puffs, each containing 200 µg budesonide (metered dose, equivalent to the 160 µg dose in the Symbicort® inhaler), twice daily)

Group 3: Formoterol alone (2 puffs, each containing 4.5 µg formoterol, twice daily)

Group 4: Inhaled a placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded.

3. The results of this study showed a synergistic effect from the combination of budesonide and formoterol.

For example, as shown in the graph titled "Symbicort Reduces No. of Severe Exacerbations/Patient/Year"[2] (Appendix 1, submitted herewith), as compared to the placebo (Group 4), treatment with formoterol alone (Group 3) increased the number of exacerbations slightly (+3%), and treatment with budesonide alone (Group 2) decreased the number of exacerbations by 12%. Thus, it would be expected that the additive effect of the

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[1] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

[2] Severe exacerbations were considered to be exacerbations requiring medical intervention, i.e., administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

budesonide/formoterol combination would be a 9% reduction in exacerbations. Instead, Group 1, treated with the budesonide/formoterol combination, exhibited a 24% reduction in exacerbations.

4. A synergistic effect was also observed in the morning peak expiratory volume (PEF) of the patients, as shown in the graph titled "Symbicort Improves Morning PEF" (Appendix 2, submitted herewith). The difference in adjusted mean change of morning PEF, as compared to the placebo, was 3.5 L/min for the patients treated with budesonide alone, 11.1 L/min for those treated with formoterol alone ($p<0.001$), and 18.3 L/min for the patients treated with the budesonide/formoterol combination, i.e., 3.7 L/min higher than the additive result that would have been expected.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

By: Christer Hultquist   Date: 2002-12-06

Christer Hultquist, M.D.

CURRICULUM VITAE

Name
Christer Hultquist

Date of birth
1 October 1946

Nationality
Swedish

Education
1977 fully qualified physician

Postgraduate training
1981 Certified. Pediatrician
1982 Certified in Pediatric Allergology

Professional appointements
Member of the Staff and Senior Registrar, Department of Pediatrics, University of Lund, 1981-1991.
Medical Adviser, Astra Draco AB, Lund, 1991-99.
AstraZeneca 1999-2000
- Global Product Physician, Pulmicort, 1999-2000
- Global Product Physician, Symbicort, June 2000 –Feb 2002
- Clinical Development Medical Director, Symbicort, March 2002

Professional associations
Swedish Pediatric Association
Swedish Pediatric Association for Allergy and Immunology
Swedish Association for Pulmonary Medicine
Swedish Association for Allergology
ERS
ATS

Lund 13 September 2002
Christer Hultquist
Christer Hultquist

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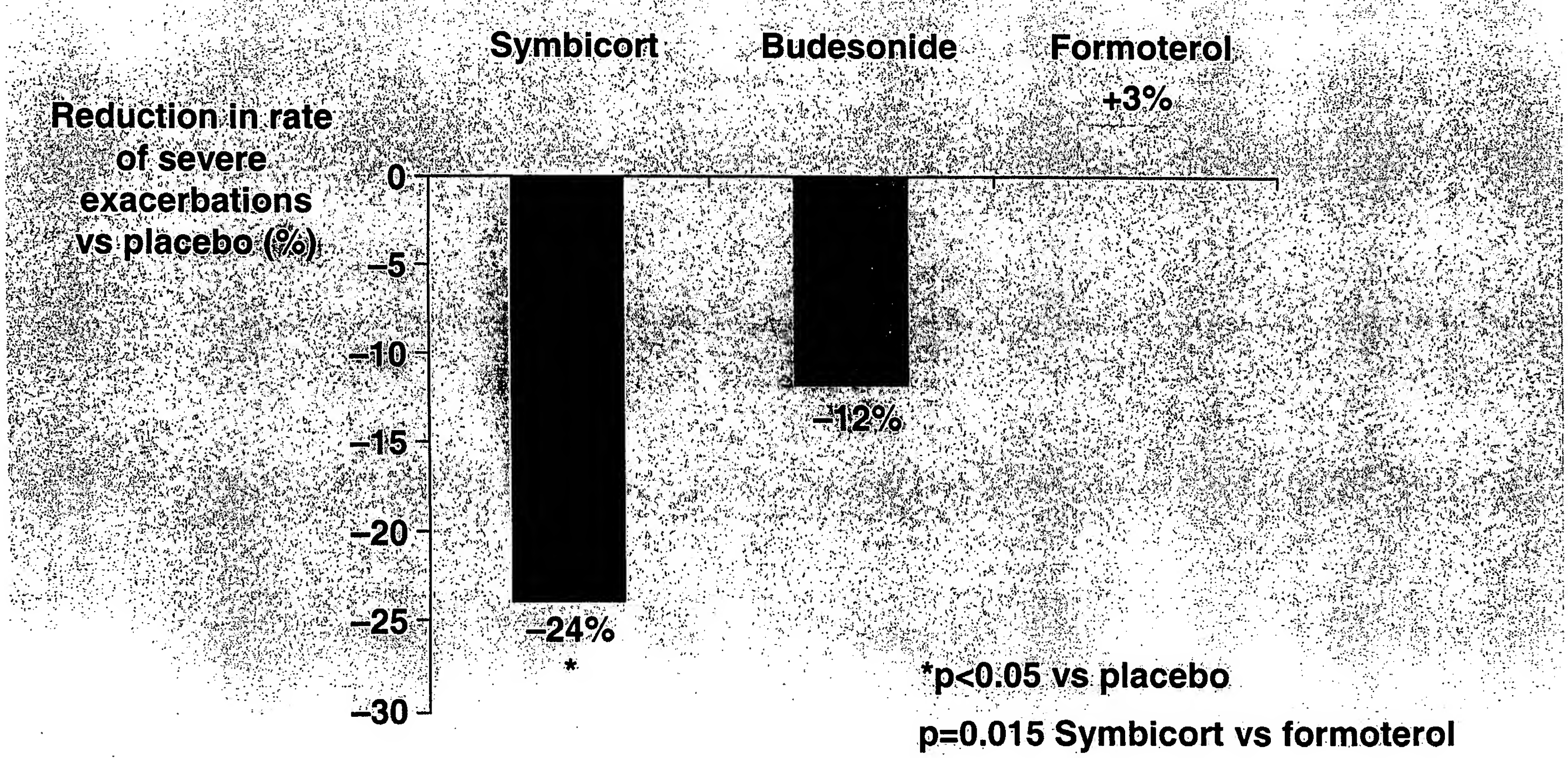
Lund 13 September 2002

Christer Hultquist

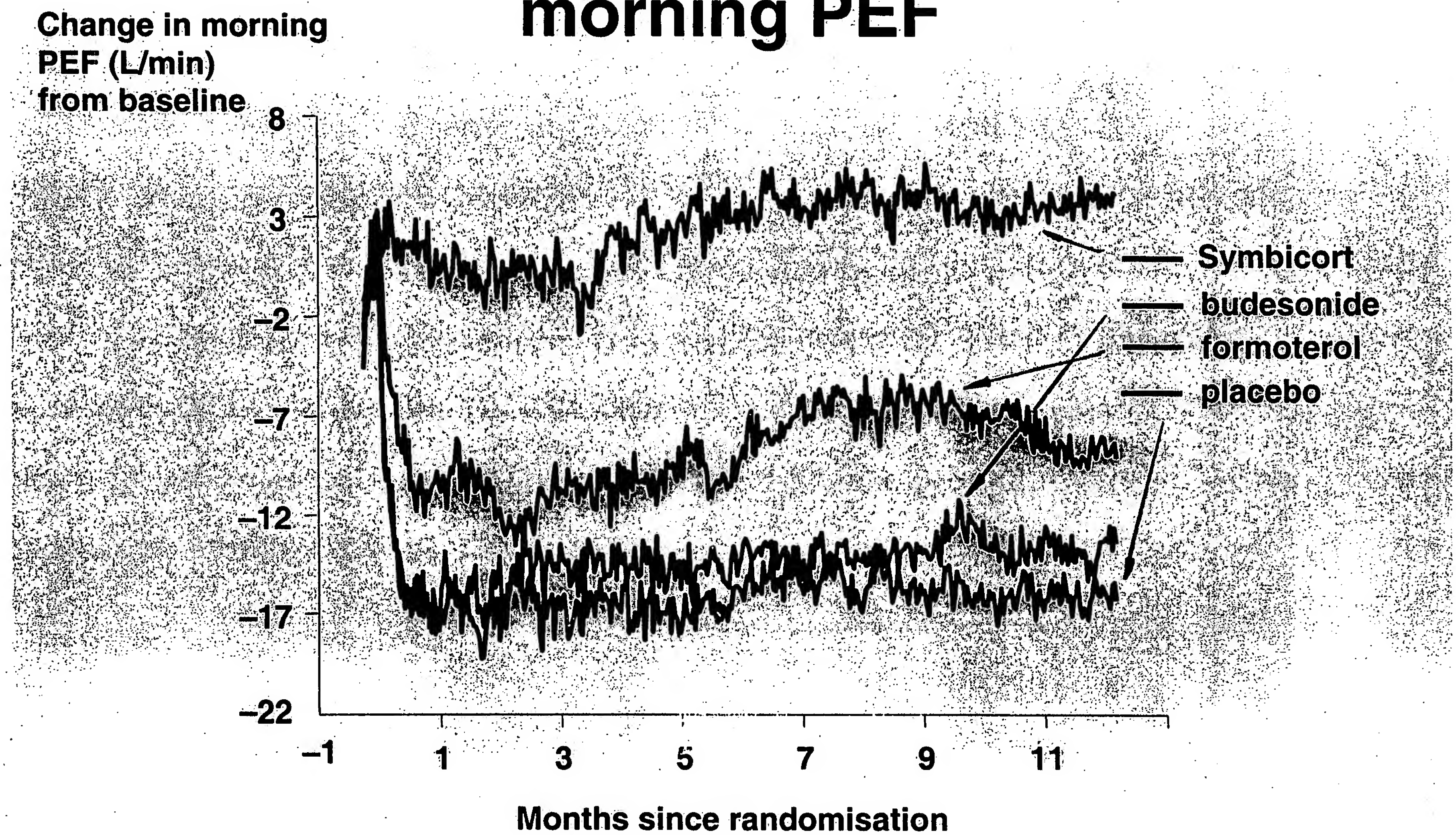
Item 7. Appendix 1

Symbicort reduces no. of severe exacerbations/patient/year



Item 7. Appendix 2

Symbicort improves morning PEF



Thorax 1998;53:129–136

Occasional reviews

Structural and inflammatory changes in COPD: a comparison with asthma

Peter K Jeffery

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. In Europe COPD and asthma, together with pneumonia, are the third most common cause of death. In North America COPD is the fourth leading cause of death, and mortality rates and prevalence are increasing. The incidence and morbidity from COPD are rising. The main risk factors are cigarette smoking and occupational exposure. Part of the reason for the slow advance in our understanding has been the difficulty of distinguishing, with certainty, the difference between subjects with COPD who may show a degree of airways reversibility and those older subjects with asthma whose reversible airflow obstruction has become more "fixed". There may also be mixtures of COPD and asthma which co-exist in any one patient (fig 1).

For the purpose of the present synopsis the definitions of COPD and asthma are those included in the recently published ERS and ATS guidelines;[1–3] there is, however, much debate and the clinical definitions are still imprecise. The difficulties of definition are compounded by the recognition that both COPD and asthma are not disease entities but, rather, each is probably a complex of conditions which contribute to airflow limitation (*syn* obstruction). In asthma, airflow limitation is usually variable over short periods of time and reversible, although an underlying irreversible component may develop when inflammation persists in association with repeated allergen or occupational exposure; extrinsic (allergic) and intrinsic (late onset) and occupational forms are recognised. In COPD the limitation, particularly to expiratory airflow, is usually, but not always, persistent and typically shows a more rapid progressive deterioration with age than is normal. Accordingly, the most recent and generally accepted definition in Europe is: "Chronic obstructive pulmonary disease (COPD) is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months".[1] Three conditions may contribute to airflow limitation to varying degrees in each patient:

(1) Chronic bronchitis (mucus hypersecretion) which is defined as the presence of chronic cough and recurrent increases in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of three months a year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes.[4–6] Chronic bronchitis can occur in the absence of airflow limitation.

(2) Adult chronic bronchiolitis (small or peripheral airways disease) which is difficult to define clinically but may be recognised by sophisticated tests of function of the small airway – that is, airways of 2 mm diameter or less.[7 8]

(3) Emphysema which is defined anatomically by permanent, destructive enlargement of airspaces distal to terminal bronchioli without obvious fibrosis.[9] However, the presence or absence of an ongoing fibrotic process is still debated (see below).

The airways in chronic bronchitis and COPD are also markedly inflamed; however, in contrast to asthma the predominant type of inflammatory cell and the main anatomical site of the lesion appear to differ.[10]

The following synopsis focuses on the structural changes and the inflammation of conducting airways and lung in COPD and briefly makes comparisons with what is known in asthma. For further details of the effects of smoking and comparisons of COPD with asthma the reader is referred elsewhere.[11–14]

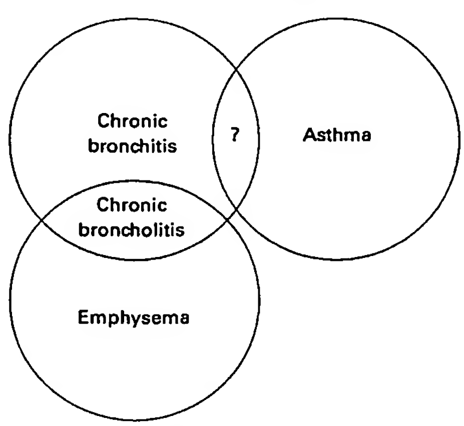


Figure 1 Airflow limitation: simplified interrelationships between COPD and asthma.

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P K Jeffery

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Pathology

PROXIMAL BRONCHI (CHRONIC BRONCHITIS)

Cough and sputum production are the symptoms most frequently experienced by smokers;

Item 1. Page 7, from "GOLD: Global Initiative for Chronic Obstructive Lung Disease; Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease" (2004)

report. Emphysema, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of two consecutive years, remains a clinically and epidemiologically useful term. However, it does not reflect the major impact of airflow limitation on morbidity and mortality in COPD patients. It is also important to recognize that cough and sputum production may precede the development of airflow limitation; conversely, some patients develop significant airflow limitation without chronic cough and sputum production.

NATURAL HISTORY

COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues. If exposure is stopped, the disease may still progress due to the decline in lung function that normally occurs with aging. Nevertheless, stopping exposure to noxious agents, even after significant airflow limitation is present, can result in some improvement in function and will certainly slow or even halt the progression of the disease.

Classification of Severity: Stages of COPD

For educational reasons, a simple classification of disease severity into four stages is recommended (**Figure 1-2**). The staging is based on airflow limitation as measured by spirometry, which is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific FEV_1 cut-points (e.g., < 80% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated.

The impact of COPD on an individual patient depends not just on the degree of airflow limitation, but also on the severity of symptoms (especially breathlessness and decreased exercise capacity) and complications of the disease. The management of COPD is largely symptom driven, and there is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms. The staging, therefore, is a pragmatic approach aimed at practical implementation and should only be

Figure 1-2. Classification of Severity of COPD

Stage	Characteristics
0: At Risk	• normal spirometry • chronic symptoms (cough, sputum production)
I: Mild COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted • with or without chronic symptoms (cough, sputum production)
II: Moderate COPD	• $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted • with or without chronic symptoms (cough, sputum production)
III: Severe COPD	• $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ predicted • with or without chronic symptoms (cough, sputum production)
IV: Very Severe COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Classification based on postbronchodilator FEV_1
FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

Item 2.

Eur Respir J 2003; 22: 874–875
DOI: 10.1183/09031936.03.00111303

European Respiratory Journal
ISSN 0903-1936

EDITORIAL

Combination therapy for chronic obstructive pulmonary disease: one size fits all?

K.F. Rabe

Without hesitation I would acknowledge that combination products with fixed doses of long-acting β-adrenoceptor agonists and inhaled corticosteroids are an established therapeutic option for asthma in patients with moderate and severe disease. These drugs have changed conceptual views of asthma treatment and may have simplified asthma management, which is probably one of their greatest merits! There is a reasonable scientific basis for the use of combination therapy [1] that convinced us that the fixed combination of bronchodilators with inhaled steroids is the treatment of choice, at least for patients that are not sufficiently controlled with a short-acting β-agonist and an inhaled steroid. I still find it puzzling that the same doses of drugs given in one inhaler should have a greater effect in these patients compared to the single components (at least in the first weeks of treatment), but that's the data and all published studies irrespective of sponsorship come to the same conclusion. As this is the evidence, I am happy to adopt this strategy.

But chronic obstructive pulmonary disease (COPD)? We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically. I can see the role of long-acting bronchodilators for the treatment of COPD, an issue that is already addressed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [2], but the use of inhaled steroids and combination therapy as in asthma? Is this a "one size fits all" strategy that is driven by commercial interests? And, were we all wrong, does this mean we no longer need to differentiate between asthma and COPD since the treatment will be the same in the end?

At this point the available evidence should probably be considered. In this issue of the *European Respiratory Journal*, P. Calverley and co-authors [3] (yes, the TRISTAN P. Calverley [4]) present the second large clinical study of 2003 that demonstrates that maintenance treatment with a fixed dose of an inhaled steroid (budesonide) and long-acting β-agonists (formoterol) in COPD improves lung function, quality of life and delays the time to first exacerbation and that this effect is more pronounced with the combination therapy than in either component alone. One-thousand and twenty-two COPD patients (with 629 or 62% completing the study) with a mean forced expiratory volume in one second (FEV1) of 36% predicted were included in this multicentre trial and were randomised to receive either budesonide or formoterol or the combination of both or placebo, with terbutaline as rescue medication. Randomisation followed a run-in period of 2 weeks during which patients were treated with 30 mg oral prednisolone and formoterol *b.i.d.*, and terbutaline as rescue medication. The primary outcomes of this trial were the time to first exacerbation and change in FEV1. The authors also recorded data on peak expiratory flow, health-related quality of life, symptoms, use of reliever medication and adverse events.

Is there anything wrong with this study? No, otherwise you would not find it in a high-quality Journal such as the *ERJ*. It is potentially an important clinical study but there are some issues that need to be highlighted to put the data into perspective. The present study is the third to assess the effect of combination therapy in COPD. However, the design differs to the other two [4, 5] as the run-in period comprises a treatment optimisation with oral steroids, leading to a significant improvement of patients with an FEV1 increase of 210 mL and a health status improvement of 4.5 units, exceeding the magic 4.0 line by 0.5 points. It is therefore correct, as stated by the authors, that in this study, combination therapy maintains the effect of treatment optimisation with reference to patients with these characteristics. However, it is surprising that the deterioration of patients occurs so rapidly (within days) in the other treatment groups, including those that were treated with budesonide only.

Compared to the other two available studies [4, 5], the long-acting β-adrenoceptor agonist alone did not affect the time to first exacerbation compared to placebo while the combination therapy clearly did [3]. The authors correctly defined an exacerbation as an episode requiring oral steroids and/or antibiotic treatment and analysed those episodes requiring steroids separately. The data seem to indicate that patients experiencing more severe exacerbations benefit the most from combination therapy and confirm, to some extent, the findings from the TRISTAN trial by the same author [4]. If the definition of a (mild) exacerbation for clinical trials also includes aggravation of symptoms, such as in the paper by SZAFRANSKI *et al.* [5], the relative effect of a long-acting bronchodilator might be more pronounced. This is also evident in the present study in which formoterol alone had a significant effect on symptoms such as shortness of breath, chest tightness and night-time awakenings. This clearly highlights the importance of definitions of exacerbations for clinical trials and calls for studies comparing the effect of maximal bronchodilation with, for example, the combination of long-acting β-adrenoceptor agonists with long-acting anticholinergics in COPD with mild and severe exacerbations as an outcome.

Does this paper tell us why combination therapy has improved efficacy in this group of COPD patients? No (see Discussion in [3]), but this paper does provide evidence that in advanced disease, after a steroid trial with measurable lung function and symptomatic improvement, combination therapy is an effective treatment option. This might also imply that physicians who are not aware of the individual risk of exacerbations in a given patient with an FEV1 <50% pred should consider an oral steroid course to help them in their decision of how to proceed with maintenance treatment.

Does this study in patients with COPD (and the other

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available evidence) suggest that combination therapy with inhaled corticosteroids and long-acing β-adrenoceptor agonists is a "one size fits all" option for all patients with a low FEV1, making the differential diagnosis between asthma and COPD redundant? This would not only result in the extinction of pulmonologists dealing with obstructive lung diseases but it would also be wrong! The role of steroids in the treatment of patients with asthma [6] is fundamentally different compared to COPD [7–11], since the perceptions of symptoms in asthma and the evidence for early intervention probably favour the use of these drugs in combination with bronchodilators in the future in even earlier stages of the disease than currently recommended. In contrast, asymptomatic COPD patients should not be treated with drugs, and this alone, amongst other considerations, clearly calls for a differentiation of these two diseases that are fundamentally different in the vast majority of patients. In advanced disease states the treatment algorithms admittedly become more similar and the present study provides additional evidence for the use of combination therapy in patients with COPD. However, all published studies, including the present paper in the *ERJ*, support the current GOLD guidelines that combination therapy with inhaled steroids and long-acting β-adrenoceptor agonists should be reserved for COPD patients with advanced disease (FEV1 <50% pred) and a history of frequent (more than one) "real" exacerbations per year [12]. For the remainder, further studies on the role of maximal bronchodilator therapy are urgently needed.

For the clinical reader of the *European Respiratory Journal*, the present paper might provide a practical approach to new patients in which the exacerbation history is not known. A steroid optimisation period for 2 weeks might not only help to differentiate between asthma and chronic obstructive pulmonary disease, it will probably help to identify chronic obstructive pulmonary disease patients who will undoubtedly benefit from combination therapy.

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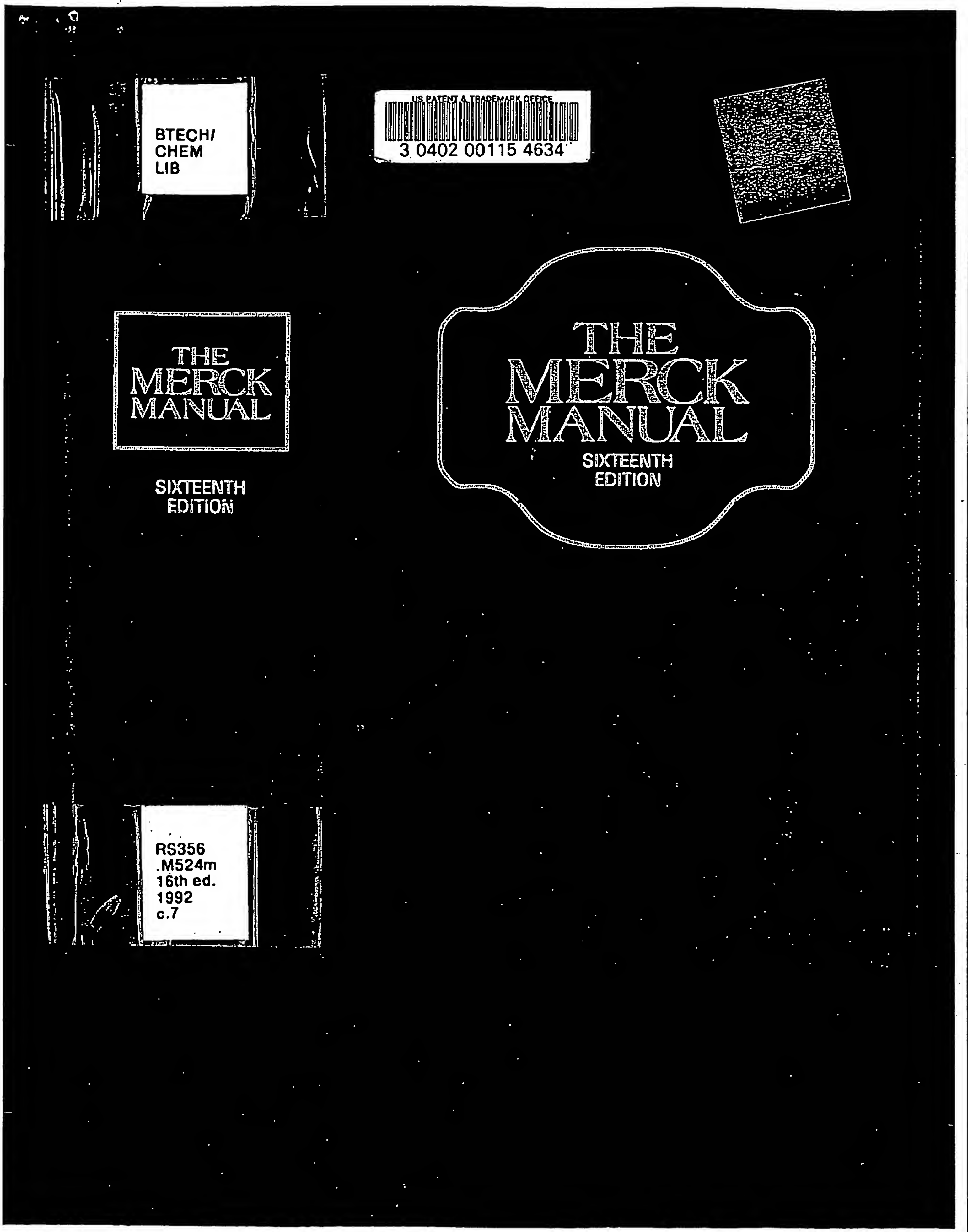
Item 3.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Pulmonary signs are few in uncomplicated acute bronchitis. Scattered high- or low-pitched rhonchi may be heard, as well as occasional crackling or moist rales at the bases. Wheezing, especially after cough, is commonly noted. Persistent localized signs suggest development of bronchopneumonia.

Serious complications are usually seen only in patients with an underlying chronic respiratory disorder. In such patients, acute bronchitis may lead to severe blood gas abnormalities (acute respiratory failure).

Diagnosis

Diagnosis is usually based on the symptoms and signs, but a chest x-ray to rule out other diseases or complications is indicated if symptoms are serious or prolonged. Arterial blood gases should be monitored when serious underlying chronic respiratory disease is present. In persons who do not respond to antibiotic therapy, or in special circumstances (eg, immunosuppression), Gram stain and sputum culture should be done to determine the causative organism.

Treatment

General: Rest is indicated until fever subsides. Oral fluids (up to 3 or 4 L/day) are urged during the febrile course. An antipyretic analgesic (eg, for adults aspirin 600 mg or acetaminophen 500 mg q 4 to 6 h; for children acetaminophen 10 to 15 mg/kg q 4 to 6 h) relieves malaise and reduces fever.

Local: Symptomatic treatment of cough is discussed in Ch. 29.

Antibiotics are indicated when there is concomitant chronic obstructive pulmonary disease, when purulent sputum is present, or when high fever persists and the patient is more than mildly ill. For adults oral tetracycline or ampicillin 250 mg q 6 is a reasonable first choice for most cases. Tetracycline should be withheld in children < 8 yr old; instead give amoxicillin 40 mg/kg/day in divided doses tid. When symptoms persist or recur, or in unusually severe disease, smear and sputum culture are indicated. The antibiotic is then chosen according to the predominant organism and its sensitivity. If *M. pneumoniae* is thought to be the causative agent, erythromycin 250 to 500 mg orally qid can be given. Trimethoprim/sulfamethoxazole (160/800 mg orally bid) may be used as an alternative to tetracycline.

CHRONIC AIRWAYS OBSTRUCTIVE DISORDERS

(Chronic Obstructive Pulmonary Disease [COPD]; Chronic Asthmatic Bronchitis)

This chapter deals with generalized persistent airways obstruction associated with varying combinations of chronic bronchitis, respiratory bronchiolitis (small airways disease), asthma, and emphysema. **Airways obstruction** is *an increased resistance to airflow during forced expiration*. Its hallmark is slowing of forced expiration, producing characteristic spirometric findings. It may result from narrowing or obliteration of airways secondary to intrinsic airways disease, from excessive expiratory collapse of airways secondary to pulmonary emphysema, from "bronchospasm" (as in asthma), or from a combination of these factors.

To avoid confusion, the following definitions are given: (1) **Chronic bronchitis** (unqualified) is *a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucus hypersecretion and certain structural changes in the bronchi*. It is characterized clinically by chronic productive cough and is most commonly associated with cigarette smoking. However, the same syndrome may result from exposure to allergens in subjects whose bronchi do not tend to constrict in a typically asthmatic fashion. (2) **Chronic obstructive bronchitis** is used when there is *disease of the small airways of sufficient degree to lead to clinically significant airways obstruction*. The term is basically a misnomer, since the underlying lesion is actually a "respiratory bronchiolitis." It is frequently associated with symptoms of chronic bronchitis. (3) **Pulmonary emphysema** is *enlargement of the airspaces distal to the terminal nonrespiratory bronchioles, accompanied by destructive changes of the alveolar walls*. **Chronic obstructive emphysema** is used

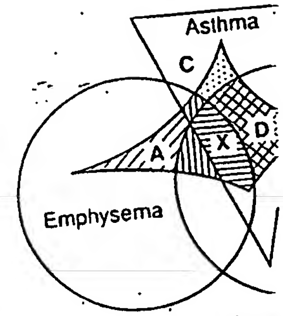

FIG. 34–1. Interrelationship of asthma, emphyse
airways obstruction. Shaded areas represent patients
struction. Patients with a relatively pure emphysematous
type of chronic obstructive bronchitis are labeled B. Gro
which is so persistent that there is clinically significant
tions with chronic asthmatic bronchitis who may show
airways obstruction but never return to normal. Persons
X. Chronic productive cough (chronic bronchitis) may

when there is *sufficient loss of lung recoil to allo*
leading to the physiologic pattern of airways obs
refers to *an underlying asthmatic problem in pa*
persistent that clinically significant chronic ai
asthmatic therapy. The symptoms of chronic b

These conditions frequently coexist and it
decide which is the major one producing the ob
to the combination of chronic obstructive b
described with the noncommittal term chron
Despite the frequent overlap of the disorders,
matic bronchitis should be distinguished from
of COPD since the course, prognosis, and re

Interrelationships between these disorders
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have sufficient airways obstructive problems
many cigarette smokers have evidence of d
develop clinically significant airways obstru
some combination of small airways disease
reversibility to their disease, suggesting that
most asthmatics, particularly those < 40 yr o
ible with therapy and that should not be cont
more persistent with age. Persistent airways
common in the elderly asthmatic. The exte
present in these chronic asthmatic bronchit

Etiology

The basic lesion of emphysema is belie
of proteolytic enzymes, which can be rele
matory process. Thus, any factor leadin
courage development of an emphysema
antiproteolytic mechanisms. Smoking ha

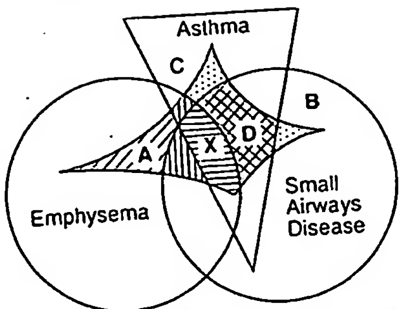


FIG. 34–1. Interrelationship of asthma, emphysema, small airways disease, and persistent airways obstruction. Shaded areas represent patients with clinically significant chronic airways obstruction. Patients with a relatively pure emphysematous-type disease are labeled A; those with a pure type of chronic obstructive bronchitis are labeled B. Group C represents patients with typical asthma, which is so persistent that there is clinically significant chronic airflow limitation. In group D are persons with chronic asthmatic bronchitis who may show considerable fluctuation in the severity of the airways obstruction but never return to normal. Persons with a totally mixed type of disease are labeled X. Chronic productive cough (chronic bronchitis) may accompany all of these syndromes.

when there is *sufficient loss of lung recoil to allow marked airways collapse on expiration, leading to the physiologic pattern of airways obstruction.* (4) **Chronic asthmatic bronchitis** refers to *an underlying asthmatic problem in patients in whom the asthma has become so persistent that clinically significant chronic airflow obstruction is present despite antiasthmatic therapy.* The symptoms of chronic bronchitis are generally also present.

These conditions frequently coexist and it may be difficult in an individual case to decide which is the major one producing the obstruction. This is particularly true in regard to the combination of chronic obstructive bronchitis and emphysema, which is often described with the noncommittal term **chronic obstructive pulmonary disease (COPD).** Despite the frequent overlap of the disorders, whenever possible persons with chronic asthmatic bronchitis should be distinguished from those with a primarily emphysematous type of COPD since the course, prognosis, and response to therapy are distinctly different.

Interrelationships between these disorders are depicted in FIG. 34–1. Some degree of emphysematous change is very common in smokers, but not all persons with emphysema have sufficient airways obstructive problems to be considered as having COPD. Similarly, many cigarette smokers have evidence of disease of the small airways, but a minority develop clinically significant airways obstructive disease. Most patients with COPD have some combination of small airways disease and emphysema, and some show a degree of reversibility to their disease, suggesting that there is an element of asthma as well. While most asthmatics, particularly those < 40 yr old, have a disease that is almost totally reversible with therapy and that should not be confused with COPD, the disease tends to become more persistent with age. Persistent airways obstruction that varies in intensity is relatively common in the elderly asthmatic. The extent of irreversible small airways damage that is present in these chronic asthmatic bronchitic patients remains uncertain.

Etiology

The basic lesion of emphysema is believed to result from the effect on the alveolar wall of proteolytic enzymes, which can be released from leukocytes participating in an inflammatory process. Thus, any factor leading to chronic alveolar inflammation would encourage development of an emphysematous lesion unless counteracted by the body's antiproteolytic mechanisms. Smoking has adverse effects on lung defenses and leads to

Item 4

Attorney's Docket No.: 06275-150003 / D 1841-3P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.*
Art Unit : 1617
Serial No. : 10/010,283
Examiner : Jennifer M. Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAN TROFAST UNDER 37 CFR §1.114(c)

I, Jan Trofast, declare as follows:

1. I have been a scientist at AstraZeneca R&D (formerly Astra AB) since 1979 in the division of Medicinal chemistry and Pharmaceutical & Analytical R&D at AstraZeneca. I received a Ph.D. in organic chemistry in 1978 from Lund Institute of Technology, Lund, Sweden. I have been studying and conducting research in the field of respiratory disorders since 1979, and I am an expert in this field. I am a co-inventor of the invention claimed in this application.

2. The invention claimed in this application features a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient, via inhalation, (i) formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) budesonide, the molar ratio of (i) to (ii) being from 1:2500 to 12:1.

3. I have read the Examiner's Answer to the Appeal Brief mailed December 29, 2003.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

March 1, 2004
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

4. I am an inventor named in the prior art reference, Carling *et al.* (WO 93/11773).

5. The subject of Carling *et al.* is the treatment of asthma with a β2 agonist (formoterol) and a steroid (budesonide) to treat a respiratory disorder such as asthma. Carling *et al.* states at page 4, lines 19-28 that the "invention relates to improvements in the treatment of mild as well as severe asthma and *other respiratory disorders*." The Examiner asserts, in the Examiner's Answer, that this mention of other respiratory disorders would have been understood by the artisan to include COPD. I cannot agree with this interpretation.

The phrase "respiratory disorders" has in fact been used in the medical literature to refer to a wide and varying range of disorders, the only common thread being an effect on the respiratory function of the patient. The lengthy list of such disorders, includes, for example, not only asthma and COPD, but also respiratory infections such as tuberculosis and bronchopulmonary aspergillosis, cough, asbestos-related disease and other diseases resulting from the inhalation of particulate matter, different forms of lung cancer, acute respiratory distress syndrome, toxic lung injury, cystic fibrosis, interstitial lung diseases (such as idiopathic pulmonary fibrosis and the like), alveolitis, and sarcoidosis (see, for example, "Respiratory Medicine," vol. 1, 3rd edition, Gibson *et al.*, *eds.*, Table of Contents, submitted herewith).

In the context of Carling *et al.*, the phrase "other respiratory disorders" was not meant to be interpreted so broadly, nor would someone in my field reading Carling *et al.* in 1998[1] have been likely to interpret it in this manner. Instead, the term "other respiratory disorders," as used by Carling *et al.*, was intended to and would have been understood to refer to respiratory disorders <u>similar to asthma i.e. mainly of bronchospastic nature.</u>

6. There exist a number of respiratory disorders that are similar to asthma in both their pathophysiological features and their treatment protocol, for example extrinsic atopic

[1] (The invention claimed in the present application is entitled to a priority date of November 23, 1998.).

asthma, extrinsic non-atopic asthma, intrinsic asthma, wheezing in children and bronchospastic cough. In some cases, these disorders are referred to collectively as "asthma." However, because they are different conditions they may also be referred to as "asthma and other respiratory disorders," as my co-inventors and I did in the Carling *et al.* reference. Buist ("Definitions," in Asthma and COPD, Barnes *et al.*, eds. London: Academic Press, 2002, pages 3-6) reports at page 3, column 1, the definition of asthma from the Expert Panel 2 Report (the current U.S. asthma guideline) as:

> a chronic inflammatory disorder of the airways...In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough...These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment...[emphasis added].

Thus a key pathophysiological feature common to these disorders is reversible airflow obstruction, which is monitored by spirometry or measurements of peak expiratory flow rate. These disorders are treated in similar fashion. They differ significantly, both in their pathophysiological features and their modes of treatment, from the wide range of non-asthma-like respiratory disorders listed above and in the medical literature. Thus, for example, these disorders differ significantly in both their pathology and their treatment from unrelated respiratory disorders such as lung cancer or asbestosis.

7. A diagnosis of asthma requires the exclusion of other causes of similar symptoms. COPD is the most common differential diagnosis in adults. The clinical features and pathophysiology of COPD and asthma indicate that there is some overlap between the conditions. For example, chronic inflammation underlies both diseases, but the nature of the inflammation differs. Both COPD and asthma have a reversible airflow obstruction component, but airflow obstruction in COPD is not fully reversible. In fact COPD is characterized by a progressive development of airflow limitation. Buist (2002) reports the definition of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: "A disease state characterized by progressive development of airflow limitation that is not fully reversible..." (Buist, page 3, column 1).

Sufferers of COPD and asthma also respond differently to specific therapies. For example, as discussed in Barnes *et al.* (*Eur. Resp. Jour.* 22:672-688, 2003) at page 672, column 2, and page 673, column 1:

> COPD is characterized by acceleration in the normal decline of lung function seen with age. The slowly progressive airflow limitation leads to disability and premature death and is <u>quite different from the variable airway obstruction and symptoms in asthma, which rarely progress in severity.</u> While COPD and asthma both involve inflammation in the respiratory tract there are marked differences in the nature of the inflammatory process, with differences in inflammatory cells, mediators, response to inflammation, anatomical distribution and response to anti-inflammatory therapy [emphasis added].

Buist further reports at page 4, column 1:

> Perhaps the single most important difference between the two diseases is the nature of the inflammation: it is primarily eosinophilic, CD4-driven in asthma and neutrophilic, CD8-driven in COPD...<u>There is ample evidence now that inhaled corticosteroids are effective against the eosinophilic inflammation that is characteristic of asthma...but largely ineffective against the primarily neutrophilic inflammation seen in COPD</u>...

There is generally a lack of efficient medication for COPD, and therefore the British Thoracic Society prepared guidelines specifically for the management of COPD. These guidelines do not include recommendations for treatment of asthma.

This evidence, considered collectively, indicates that COPD would not be considered to be a respiratory disorder similar to asthma by those of skill in the art.

8. Minor symptoms of COPD, for example bronchial constriction, are reversible and generally treatable by a bronchodilator such as a β2 agonist, an anticholinergic, or a theophylline. These minor reversible symptoms are similar to asthmatic symptoms. The major symptoms of COPD, however, include <u>exacerbations</u> that were <u>not</u> treatable by the classes of drugs that existed at the time of filing of Carling *et al.* (December 1991). The level

of skill in the art of treating COPD and asthma in 1991, at the time Carling *et al.* was written, was such that an expert in the field would have predicted that treatment of COPD with a β2-agonist and corticosteroid combination would be unsuccessful, particularly for the relief of exacerbations that lead to progressive airflow obstruction. As a result, at the time of the Carling *et al.* reference my co-inventors and I did not contemplate using our β2 agonist/corticosteroid combination to treat COPD.

Calverley *et al.* (*Eur. Resp. J.* 22:912-919, 2003) report the successful prevention of exacerbations in COPD patients using a combination of inhaled corticosteroid (budesonide) and β2 agonist (formoterol). Table 3 of Calverley *et al.* shows that the combination of budesonide and formoterol reduces the number of exacerbations more effectively than either budesonide or formoterol alone. Table 3 shows that the number of exacerbations per year (mean rate per patient per year) was 1.80 during treatment with placebo and a near-equivalent 1.85 during treatment with the β2 agonist formoterol. Exacerbations were mildly reduced following treatment with the corticosteroid budesonide (1.60 mean rate per patient per year) although this decrease was still not significant as compared to treatment with placebo. Treatment with the combination of budesonide and formoterol reduced the rate of exacerbations to 1.38, a significant reduction as compared to treatment with placebo. This result was surprising given the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone. The authors offer a biological explanation for this result, saying "[i]t...seems that formoterol and budesonide in combination are more effective at reducing proliferation of airway smooth muscle than either drug alone, as a result of synchronised cellular signalling..." (page 918, column 2).

Rabe *et al.* (*Eur. Respir. J.*, 22:874-875, 2003) responds to the Calverley study in an editorial published in the same journal issue as Calverley *et al.*:

> We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically. I can see the role of long-acting bronchodilators for the treatment of COPD, an issue that is already addressed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines... but the use of inhaled steroids and combination therapy as in asthma? Is this a "one size fits all"

> strategy that is driven by commercial interests? And were we all wrong, does this mean we no longer need to differentiate between asthma and COPD...? [Rabe, page 874, column 1].

Thus, asthma and COPD are still, as they were at the time of the Carling *et al.* reference and at the time of the present invention, and even in light of the Calverley study, considered by those of skill in the art to be very different diseases that require very different treatment protocols. They cannot properly be linked or considered as similar disorders, as they have as little in common as most of the other "respiratory disorders" listed in paragraph 5 above.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 24 Feb. 2004

Jan Trofast
Jan Trofast

Item 5

L28 ANSWER 5 OF 8 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB In four patients, men of 64, 66 and 69 years old and a woman of 65 years, who suffered from **chronic obstructive pulmonary disease** (**COPD**) and used inhalation corticosteroids in a relatively high dose (800-1600 .mu.g of **budesonide** per day), a pulmonary infection was diagnosed caused by Mycobacterium malmoense (the first two patients) and Aspergillus (the other two) respectively. Inhalation corticosteroids are of great importance in the treatment of asthmatic patients. Their place in the treatment of patients with **COPD** is much less clear. The patients did not have an immunological deficiency or anatomical pulmonary or bronchial deformation which could have explained the occurrence of these infections. The high dosages of inhalation corticosteroids may have been involved in the cause of these infections by suppressing the T-cell response locally. In view of this, longterm inhalation corticosteroid treatment should be prescribed in **COPD** patients only if the efficacy of the medication has been proved in the individual patient involved.

TI [Opportunistic lung infection in patients with **chronic obstructive pulmonary disease**; a side effect of inhalation corticosteroids].
OPPORTUNISTISCHE LONGINFECTIES BIJ PATIENTEN MET CHRONISCHE OBSTRUCTIEVE LONGZIEKTE; EEN BIJWERKING VAN INHALATIECORTICOSTEROIDEN?.

SO Nederlands Tijdschrift voor Geneeskunde, (**1996**) 140/2 (94-98).
ISSN: 0028-2162 CODEN: NETJAN

AB In four patients, men of 64, 66 and 69 years old and a woman of 65 years, who suffered from **chronic obstructive pulmonary disease** (**COPD**) and used inhalation corticosteroids in a relatively high dose (800-1600 .mu.g of **budesonide** per day), a pulmonary infection was diagnosed caused by Mycobacterium malmoense (the first two patients) and Aspergillus (the other two). . . Inhalation corticosteroids are of great importance in the treatment of asthmatic patients. Their place in the treatment of patients with **COPD** is much less clear. The patients did not have an immunological deficiency or anatomical pulmonary or bronchial deformation which could. . . these infections by suppressing the T-cell response locally. In view of this, longterm inhalation corticosteroid treatment should be prescribed in **COPD** patients only if the efficacy of the medication has been proved in the individual patient involved.

CT Medical Descriptors:
*chronic . . . drug therapy
*lung infection: SI, side effect
*opportunistic infection: SI, side effect
adult
aged
article
aspergillus
case report
drug efficacy
female
human
male
mycobacterium
prescription
thorax radiography
*corticosteroid: DT, drug therapy

Item 6. Exhibit C

To Colin 7/11-01

EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DENNIS E. NIEWOEHNER, M.D., MARCIA L. ERBLAND, M.D., ROBERT H. DEUPREE, PH.D., DOROTHEA COLLINS, SC.D., NICHOLAS J. GROSS, M.D., PH.D., RICHARD W. LIGHT, M.D., PAULA ANDERSON, M.D., AND NANCY A. MORGAN, R.PH., M.B.A., FOR THE DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY GROUP*

ABSTRACT

Background and Methods Although their clinical efficacy is unclear and they may cause serious adverse effects, systemic glucocorticoids are a standard treatment for patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD). We conducted a double-blind, randomized trial of systemic glucocorticoids (given for two or eight weeks) or placebo, in addition to other therapies, for exacerbations of COPD. Most other care was standardized over the six-month period of follow-up. The primary end point was treatment failure, defined as death from any cause or the need for intubation and mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy.

Results Of 1840 potential study participants at 25 Veterans Affairs medical centers, 271 were eligible for participation and were enrolled; 80 received an eight-week course of glucocorticoid therapy, 80 received a two-week course, and 111 received placebo. About half the potential participants were ineligible because they had received systemic glucocorticoids in the previous 30 days. Rates of treatment failure were significantly higher in the placebo group than in the two glucocorticoid groups combined at 30 days (33 percent vs. 23 percent, $P=0.04$) and at 90 days (48 percent vs. 37 percent, $P=0.04$). Systemic glucocorticoids (in both groups combined) were associated with a shorter initial hospital stay (8.5 days, vs. 9.7 days for placebo; $P=0.03$) and with a forced expiratory volume in one second that was about 0.10 liter higher than that in the placebo group by the first day after enrollment. Significant treatment benefits were no longer evident at six months. The eight-week regimen of therapy was not superior to the two-week regimen. The patients who received glucocorticoid therapy were more likely to have hyperglycemia requiring therapy than those who received placebo (15 percent vs. 4 percent, $P=0.002$).

Conclusions Treatment with systemic glucocorticoids results in moderate improvement in clinical outcomes among patients hospitalized for exacerbations of COPD. The maximal benefit is obtained during the first two weeks of therapy. Hyperglycemia of sufficient severity to warrant treatment is the most frequent complication. (N Engl J Med 1999;340:1941-7.)

PATIENTS with chronic obstructive pulmonary disease (COPD) frequently have exacerbations that require hospitalization. Hospital treatment for this common condition is associated with high costs and relatively poor outcomes.[1] In addition to antibiotics, oxygen, and bronchodilators, most hospitalized patients receive systemic glucocorticoids. Less severely ill patients often receive oral glucocorticoids as outpatients.

Systemic glucocorticoids improve outcomes in patients with acute asthma,[2] but their clinical efficacy in the treatment of COPD is less clear. Two small trials suggested that several days of therapy with systemic glucocorticoids improved the forced expiratory volume in one second (FEV_1) during exacerbations of COPD.[3,4] Another trial found that a single dose of methylprednisolone did not improve spirometric results over the succeeding five hours.[5] None of these trials were explicitly designed to evaluate clinical outcomes. The role of systemic glucocorticoids in patients with stable COPD is similarly unclear.[6]

Adverse effects of the short-term administration of systemic glucocorticoids include secondary infections, hyperglycemia, and a range of mood and behavioral changes.[7] Long-term therapy may cause osteoporosis, cataracts, hypertension, myopathy, and adrenal insufficiency.

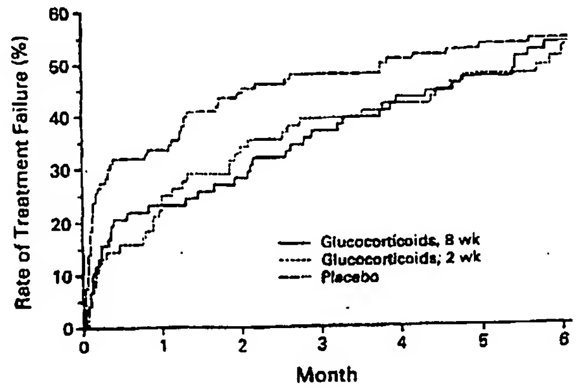
We conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of systemic glucocorticoids for exacerbations of COPD. The principal objective was to determine rates of treatment failure. A secondary goal was to determine the optimal duration of treatment.

METHODS

The Human Rights Committee of the Veterans Affairs Cooperative Studies Program and the institutional review boards of the participating medical centers approved this study. All patients gave written informed consent.

From the Veterans Affairs medical centers in Minneapolis (D.E.N.), Little Rock, Ark. (M.L.E., P.A.), Hines, Ill. (N.J.G.), and Long Beach, Calif. (R.W.L.); the Cooperative Studies Program Coordinating Center, West Haven, Conn. (R.H.D., D.C.); and the Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M. (N.A.M.). Address reprint requests to Dr. Niewoehner at the Pulmonary Section (111N), Veterans Affairs Medical Center, 1 Veterans Dr., Minneapolis, MN 55417, or at niewo001@maroon.tc.umn.edu.

*Other investigators who participated in the study are listed in the Appendix.



No. at Risk				
Glucocorticoids, 8 wk	80	61	50	21
Glucocorticoids, 2 wk	80	59	48	20
Placebo	111	74	58	39

Figure 1. Kaplan–Meier Estimates of the Rate of First Treatment Failure at Six Months, According to Treatment Group.

glucocorticoids (12 percent), and 5 assigned to eight weeks of glucocorticoids (6 percent). Follow-up data were complete for 19 of these 25 patients. All available data were included in the analyses. On the basis of counts of returned study capsules, the compliance rate was 89 percent in the placebo group, 85 percent in the two-week glucocorticoid group, and 87 percent in the eight-week glucocorticoid group.

Primary Outcomes

Figure 1 shows Kaplan–Meier estimates of rates of first treatment failure for the three study groups, and Table 2 shows the reasons for treatment failure at 30, 90, and 182 days. At least one treatment failure occurred in approximately half the patients. Intensification of therapy was the most common reason for treatment failure, accounting for 70 percent of the total failures at 30 days, 62 percent at 90 days, and 58 percent at 182 days. When therapy was intensified, physicians administered open-label systemic glucocorticoids in more than 75 percent of cases.

The trial did not demonstrate equivalence of outcomes at any time. When the upper limits of one-sided confidence intervals are used to compare failure rates between groups, the results show that the withholding of glucocorticoids may have increased treatment-failure rates by as much as 20 percent at 30 days, 21 percent at 90 days, and 12 percent at 182 days. All values exceeded the limit of 7.5 percent set by the protocol.

As compared with placebo, glucocorticoids significantly reduced the rate of first treatment failure at 30 days (23 percent vs. 33 percent, $P=0.04$) and 90 days (37 percent vs. 48 percent, $P=0.04$) (Table 2). Treatment-failure rates did not differ significantly at six months (51 percent in the combined glucocorticoid groups vs. 54 percent in the placebo group, $P=0.58$). The duration of glucocorticoid therapy (two weeks or eight weeks) had no significant effect on the rate of treatment failure at any time.

Length of Hospitalization

The average length of the initial hospitalization was significantly longer in the placebo group than in the combined glucocorticoid groups (9.7 vs. 8.5 days, $P=0.03$). After the initial hospitalization, patients in the placebo group spent an average of 2.0 days in the hospital because of COPD, as compared with 1.9 days for patients in the glucocorticoid groups ($P=0.98$). Glucocorticoid-treated patients, on average, spent more time in the hospital for reasons other than COPD than did patients receiving placebo (4.4 vs. 1.2 days, $P=0.07$).

Spirometric Findings

FEV_1 improved significantly faster in the patients who received systemic glucocorticoids than in those who received placebo (Fig. 2). The maximal difference, approximately 0.10 liter, was evident by the first day after enrollment. By the end of two weeks, FEV_1 did not differ significantly between the active-treatment and placebo groups.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 271 PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.*

CHARACTERISTIC	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)
Age — yr	67.8±10.0	67.1±10.6	68.1±6.8
Male sex — no.	111	80	77
White race — no.	99	59	68
Cough — no. (%)	65 (59)	41 (51)	43 (54)
Sputum production — no. (%)	74 (67)	54 (68)	52 (65)
Wheezing — no. (%)	98 (88)	70 (88)	72 (90)
No. of chest colds per year — no. (%)			
None	17 (15)	17 (21)	14 (18)
1 or 2	64 (58)	51 (64)	50 (62)
≥3	30 (27)	12 (15)	16 (20)
Smoked in past 3 mo — no. (%)	56 (50)	42 (52)	40 (50)
Total cigarette smoking — pack-yr	77.0±35.5	67.3±31	80.9±43.8†
Regular medications — no. (%)			
Inhaled beta-adrenergic agonist	96 (86)	66 (83)	72 (90)
Inhaled anticholinergic drug	81 (73)	47 (59)	58 (72)
Oral beta-adrenergic agonist	12 (11)	4 (5)	7 (9)
Theophylline	37 (33)	26 (32)	30 (38)
Inhaled glucocorticoids	49 (44)	39 (49)	40 (50)
Use of oxygen at home — no. (%)	20 (18)	12 (15)	15 (19)
Hospitalization for COPD in previous 2 yr — no. (%)	73 (66)	51 (64)	60 (75)
Prior use of systemic glucocorticoids — no. (%)	52 (47)	30 (38)	46 (58)†
Other illnesses — no. (%)			
Diabetes mellitus	5 (5)	12 (15)	11 (14)†
History of ulcer	23 (21)	19 (24)	16 (20)
Hypertension	44 (40)	39 (49)	39 (49)
Disabling heart disease	13 (12)	8 (10)	8 (10)
Disabling arthritis	12 (11)	10 (12)	15 (19)
History of psychiatric disorder requiring hospitalization	13 (12)	9 (11)	9 (11)
FEV_1 — ml‡	750±271	772±286	785±288
Time from presentation to randomization — hr	3.7±2.6	3.8±2.6	3.7±2.2

*Plus–minus values are means ±SD.

†P≤0.05 for differences among groups by analysis of variance for continuous variables and by the chi-square test for categorical variables.

‡Data were available for 101 patients in the placebo group, 73 in the two-week glucocorticoid group, and 72 in the eight-week glucocorticoid group.

to identify variables that predicted treatment failure within six months.[15] All reported P values are two-tailed.

RESULTS

Enrollment began in November 1994 and concluded in October 1996, one year ahead of schedule. On the basis of interim analyses, the Veterans Affairs Cooperative Studies Evaluation Committee recommended termination of enrollment at that time.

Study Population

A total of 1840 potential patients at 25 Veterans Affairs medical centers were screened for the study, of whom 271 were found to be eligible and were enrolled. The enrollment rate was lower than had been projected,[10] largely because of a substantial decline in admissions for COPD throughout the Veterans Affairs medical system and an unexpectedly high rate of exclusion because of recent use of systemic glucocorticoids. Among the patients who were screened, 49.9 percent had taken systemic glucocorticoids in the previous 30 days. Other common reasons for exclusion included unwillingness or inability to participate (23.2 percent), a history of less than 30 pack-years of smoking (14.6 percent), and coexisting medical conditions expected to limit survival (18.4 percent).

Eighty patients were assigned to receive glucocorticoid therapy for eight weeks, 80 were assigned to receive glucocorticoid therapy for two weeks, and 111 were assigned to receive placebo. The three treatment groups were similar with respect to base-line characteristics (Table 1). There were small differences in total pack-years of cigarette smoking, prior use of systemic glucocorticoids, and the prevalence of diabetes mellitus.

Discontinuation of Study Drugs and Compliance

Study drugs were discontinued for reasons other than a primary end point in 10 patients assigned to placebo (9 percent), 10 assigned to two weeks of

Study Design

We designed this study to assess the equivalence of two approaches to the treatment of COPD.[8,9] Systemic glucocorticoids are the standard therapy for hospitalized patients with COPD, even though they have adverse effects. Therefore, the withholding of glucocorticoids may be viewed as an experimental intervention associated with *no* glucocorticoid-related complications. The planning committee settled on a 7.5 percent absolute difference in the rate of treatment failure as the clinically meaningful upper limit. In other words, withholding glucocorticoids would be considered the preferred treatment if the results showed a difference in the failure rate (the rate with placebo minus the rate with active treatment) of 7.5 percent or less. The secondary objective was to assess the equivalence of two different periods of therapy (two and eight weeks). The follow-up period lasted for six months from the time of enrollment. A detailed description of the rationale for the study, its design, the protocol, and the planned analyses is provided elsewhere.[10]

Study Population

All patients admitted to participating Veterans Affairs medical centers for exacerbations of COPD were potential subjects. The principal inclusion criteria were a clinical diagnosis of exacerbation of COPD, an age of 50 years or more, a history of 30 pack-years or more of cigarette smoking, and either an FEV_1 of 1.50 liters or less or an inability to undergo spirometry because of dyspnea. The principal exclusion criteria were a diagnosis of asthma, use of systemic glucocorticoids within the preceding 30 days, coexisting medical conditions that made survival for at least 1 year unlikely, and inability to give informed consent. We obtained base-line data on respiratory disease and other pertinent aspects of the medical history by means of a questionnaire.[11]

Treatments

We randomly assigned patients within 12 hours after presentation to one of three treatment groups. The first group received eight weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Kalamazoo, Mich.) (given in a dose of 125 mg every 6 hours for 72 hours) followed by once-daily oral prednisone (60 mg on study days 4 through 7, 40 mg on days 8 through 11, 20 mg on days 12 through 43, 10 mg on days 44 through 50, and 5 mg on days 51 through 57). The second group received two weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (125 mg every 6 hours for 72 hours), followed by oral prednisone (60 mg on days 4 through 7, 40 mg on days 8 through 11, and 20 mg on days 12 through 15), with placebo capsules on study days 16 through 57. The third group received placebo, consisting of an equivalent volume of intravenous 5 percent dextrose solution (every 6 hours for 72 hours), followed by placebo capsules on days 4 through 57. Randomization was stratified according to hospital with a permuted-block scheme; 40 percent of the patients were assigned to the placebo group, 30 percent to the eight-week glucocorticoid group, and 30 percent to the two-week glucocorticoid group.

The Veterans Affairs Cooperative Studies Clinical Research Pharmacy Coordinating Center distributed the study medications. Designated research pharmacists dispensed the intravenous medications in a blinded fashion. All patients received the same number of identical-appearing study capsules in blister packs. We assessed compliance on the basis of capsule counts.

The patients remained hospitalized for at least three days for intravenous therapy, after which they received capsules of prednisone or placebo for eight weeks. Hospital staff decided the date of discharge after three days of intravenous therapy. All the patients received a broad-spectrum antibiotic for seven days. For the entire six-month period, the patients were required to use an inhaled β-adrenergic agonist (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), inhaled ipratropium bromide (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), and starting on day 4, inhaled triamcinolone acetonide (eight puffs daily in divided doses) or its equivalent. Use of theophylline, high-dose inhaled glucocorticoids (more than eight puffs daily of triamcinolone acetonide or its equivalent), and open-label systemic glucocorticoids was not allowed. Treatment was considered to have failed if any of the forbidden medications were prescribed. Other medications were permitted according to medical need. We evaluated the patients on each of the first three hospital days and at two weeks, eight weeks, and six months. We continued to obtain follow-up data for patients in whom the study drug had been withdrawn because of treatment failure or for other reasons. If a patient missed a visit, we collected data by mail, telephone, or a review of medical records.

End Points

The primary end point, a first treatment failure, was defined as death from any cause or the need for intubation and mechanical ventilation, readmission because of COPD, or intensification of pharmacologic therapy. The patients' primary physicians made all the clinical decisions. We defined intensification of pharmacologic therapy as the prescription of open-label systemic glucocorticoids, high-dose inhaled glucocorticoids (more than eight puffs per day of triamcinolone acetonide or its equivalent), theophylline, or any combination of these three therapies. When multiple failures occurred on the same day, the assignment to the category of first failure was hierarchical, in the following descending order: death, intubation, readmission, and intensification of therapy. When a primary end point (other than death) was reached, the study treatment was terminated, and usual medical care was resumed.

Secondary end points were a change in FEV_1, the length of the hospital stay, and death from any cause during the six months of follow-up. The patients underwent spirometry at base line; on days 1, 2, and 3; and at the two-week, eight-week, and six-month visits. All centers performed spirometry (model 922, SensorMedics, Yorba Linda, Calif.) according to standard recommendations.[12] We calculated the initial hospital stay as the period from the day of admission to the day of discharge or transfer to an extended-care facility.

Complications

We evaluated the patients for any possible adverse effects of treatment at each visit. As described elsewhere,[10] the diagnosis of hyperglycemia, hypertension, secondary infection, upper gastrointestinal bleeding, or acute psychiatric illness required a consultation, an invasive procedure, or initiation of a specific therapy. We also questioned the patients about other possible adverse events.

Statistical Analysis

The base-line characteristics of the patients in the three treatment groups were compared by means of analysis of variance for continuous variables and the chi-square test for categorical variables.[13] All comparisons of results were based on the intention-to-treat principle. Treatment comparisons were made with the use of a two-step procedure: if the findings for the two-week and the eight-week groups were found to be equivalent, these two groups were combined into a single active-treatment group for comparison with placebo. Comparisons were made at 30, 90, and 182 days after the start of treatment. Treatment failure, the primary end point, was analyzed with use of the upper limit of a one-sided 95 percent confidence interval to determine therapeutic equivalence[14] and a two-sided log-rank test to compare differences between curves for the cumulative failure rate.[15] Values for FEV_1 in the glucocorticoid and placebo groups were compared by analysis of variance, and hospital stays were compared with use of the Wilcoxon two-sample rank test.[13] A complication rate was defined as the proportion of patients who had one or more episodes of a complication during the six months of follow-up. Logistic-regression analysis was used

TABLE 2. CUMULATIVE PRIMARY OUTCOMES ACCORDING TO TREATMENT ASSIGNMENT.

OUTCOME	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)	P VALUE*
	number (percent)			
30 days				
Death	3 (3)	0	2 (2)	
Intubation	3 (3)	2 (2)	1 (1)	
Readmission for COPD	5 (5)	4 (5)	2 (3)	
Intensification of therapy	26 (23)	13 (16)	13 (16)	
Total	37 (33)	19 (24)	18 (22)	0.04
90 days				
Death	4 (4)	2 (2)	2 (2)	
Intubation	3 (3)	3 (4)	1 (1)	
Readmission for COPD	13 (12)	8 (10)	6 (8)	
Intensification of therapy	33 (30)	17 (21)	20 (25)	
Total	53 (48)	30 (38)	29 (36)	0.04
182 days				
Death†	4 (4)	2 (2)	3 (4)	
Intubation	3 (3)	3 (4)	2 (2)	
Readmission for COPD	17 (15)	12 (15)	13 (16)	
Intensification of therapy	36 (32)	22 (28)	24 (30)	
Total	60 (54)	39 (49)	42 (52)	0.58

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the log-rank test.

†Only deaths that were counted as primary outcomes are listed. The total numbers of deaths during six months of follow-up were 11 in the placebo group and 13 in the glucocorticoid groups.

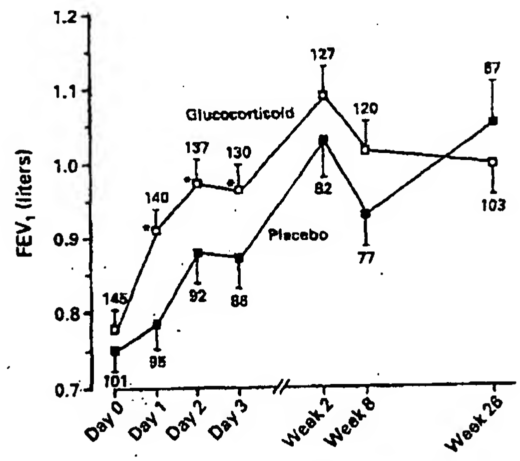


Figure 2. Mean Forced Expiratory Volume in One Second (FEV_1) at Selected Times According to Treatment Group.

The two-week and eight-week glucocorticoid groups have been combined. The numbers at each time point are the numbers of patients in each group for whom data were available. The asterisks denote $P<0.05$ for the comparison with placebo. The bars indicate standard errors.

Death from All Causes

Over the six months of follow-up, 11 of the 111 patients receiving placebo and 13 of the 160 receiving glucocorticoids died (P=0.61). Seven deaths in the placebo group and six in the combined glucocorticoid groups were attributed to COPD.

Complications

Table 3 shows the reported complications for each treatment group over the six months. A greater proportion of patients in the glucocorticoid groups than in the placebo group had hyperglycemia requiring treatment (15 percent vs. 4 percent, P=0.002). Twenty-two of the 24 episodes in the glucocorticoid groups occurred during the first 30 days of follow-up. Sixteen of the 24 glucocorticoid-treated patients with hyperglycemia were known to have diabetes. The patients who received glucocorticoids also had more adverse events classified as "other" (P=0.04); these included 41 separate symptoms or conditions, most of which were not thought to be caused by glucocorticoids. Reported rates of secondary infection did not differ significantly among the three groups, but the eight-week glucocorticoid group had the highest proportion of patients with serious infections. Eleven of the patients in this group were rehospitalized with a primary diagnosis of infection; 9 of the 11 had pneumonia. Only four patients in the placebo group and one in the two-week glucocorticoid group were rehospitalized for infection.

TABLE 3. COMPLICATIONS OF TREATMENT DURING THE SIX-MONTH FOLLOW-UP PERIOD.

COMPLICATION	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)	P VALUE*
	number (percent)			
Hyperglycemia	4 (4)	14 (18)	10 (12)	0.002
Gastrointestinal bleeding	5 (5)	0	3 (4)	0.21
Secondary infection	19 (17)	12 (15)	18 (22)	0.73
Hypertension	4 (4)	6 (8)	4 (5)	0.33
Psychiatric disorder	3 (3)	5 (6)	2 (2)	0.47
Other adverse events†	16 (14)	18 (22)	21 (26)	0.04

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the chi-square test.

†This category includes 41 different symptoms or conditions.

Subgroup Analyses

As specified by the protocol, we performed subgroup analyses for the following variables: base-line FEV_1, theophylline use before randomization, hospi-

talization because of COPD in the previous two years, a history of cough, a history of wheezing, a history of sputum production, and a history of chest colds. Multiple logistic regression indicated that a base-line value for FEV_1 that was less than the median value of 0.73 liter predicted a higher rate of treatment failure at 182 days (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 3.1), as did theophylline use before randomization (odds ratio, 2.3; 95 percent confidence interval, 1.3 to 4.0). Only prior hospitalization because of COPD had a significant interaction with the treatment assignment ($P=0.01$). Treatment with glucocorticoids was associated with a more favorable outcome in the group of 184 patients who had previously been hospitalized because of COPD than in the group of 87 with no history of hospitalization because of COPD (odds ratio, 4.6; 95 percent confidence interval, 1.4 to 14.8). In the group of previously hospitalized patients, the failure rate at six months was 66.7 percent for those who received placebo and 49.5 percent for those who received glucocorticoids.

DISCUSSION

We found that the withholding of systemic glucocorticoids was not equivalent to active treatment for hospitalized patients with COPD. Glucocorticoids were marginally superior to placebo in reducing rates of treatment failure at 30 and 90 days, but not at 6 months. Glucocorticoid therapy also shortened the initial hospital stay by an average of 1.2 days. This difference may be an underestimate, because the protocol required a hospital stay of at least three days and because some patients assigned to receive placebo also received open-label glucocorticoids.

Glucocorticoid-induced improvements in FEV_1 provide a plausible basis for the better clinical outcomes. The magnitude of the early effect of treatment on FEV_1, approximately 0.10 liter, is similar to that found in a previous study.[3] More patients received open-label glucocorticoids as the study progressed, so we may have underestimated the true differences at later times.

Hyperglycemia of sufficient severity to require therapy was the major complication of glucocorticoids that we identified. This finding may be due in part to the higher proportions of patients with diabetes in the glucocorticoid groups than in the placebo group, but hyperglycemia is a known complication of glucocorticoid therapy.[16,17] We also noted a trend toward longer hospital stays for causes other than COPD in both glucocorticoid groups. Careful review of these data revealed an unusual number of infections requiring hospital readmission in the eight-week glucocorticoid group. Controlled trials of treatment for other diseases have shown an increased risk of serious infection in patients receiving systemic glucocorticoids.[16,18]

Osteoporosis was not evaluated in this trial, but even relatively brief courses of systemic glucocorticoids cause reductions in trabecular bone mineral density.[19] The cumulative effects of long-term therapy confer a substantial risk of painful vertebral fractures and other long-term complications.[7,20]

Intensification of pharmacologic therapy accounted for more than half of all treatment failures at six months and an even higher proportion during the early weeks of follow-up in our study. Open-label glucocorticoids were administered in most of these cases. Thus, the principal consequence of withholding glucocorticoids in patients receiving placebo was to delay their administration to about half of these patients. The other half recovered and received no glucocorticoids during the full six months of follow-up.

The overall exposure to glucocorticoids among patients hospitalized for COPD would be substantially decreased if the drug were withheld until it was evident that other therapy had failed. The disadvantages of this option are a delay in the administration of effective therapy to patients with severe dyspnea and a prolongation of the average hospital stay by slightly more than a day.

Recent use of systemic glucocorticoids disqualified half the patients screened for this study, and these patients might have had different responses to glucocorticoids. We designed this study specifically for hospitalized patients, reasoning that the effect of treatment would be most evident in the sickest patients. However, systemic glucocorticoids are also frequently used for outpatient treatment of COPD, and the clinical profiles of nonhospitalized patients may be different.

We conclude that systemic glucocorticoids decrease the rate of treatment failure by about 10 percentage points for up to 90 days when used for patients hospitalized with exacerbations of COPD. A two-week regimen was as effective as an eight-week regimen; this result was consistent with those of small trials involving patients with acute asthma.[21,22] In addition, subgroup analyses suggest that the treatment benefit may be restricted largely to patients who have previously been hospitalized because of COPD.

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APPENDIX

The other study participants were as follows: Planning Committee: S. Weiss, J. Stoller, I. Tager, M. Antonelli, and M. Buchanan; Data Monitoring Board: D. Dantzker (chair), D. Tashkin, R. Simon, and M. Lebowitz; Pharmacy coordinator: J. Day; investigators at individual Veterans Affairs medical centers: J. Curtis (principal investigator) and C. Siegert, Ann Arbor, Mich.; G. Emmanuel (coprincipal investigator), S. Carranza (coprincipal investigator), and D. Johnson, Bay Pines, Fla.; P. Romano (coprincipal

investigator), P. Kaul (coprincipal investigator), and R. Varano, Brooklyn, N.Y.; S. Sethi (principal investigator) and P. DiMarzia, Buffalo, N.Y.; R. Keller, Hines, Ill.; M. Reinoso (principal investigator) and P. Guillet, Houston; G. Bhaskar (principal investigator) and H. Hermesman, Lake City, Fla.; G. San Pedro (coprincipal investigator) and L. Frazier, Little Rock, Ark.; J. Despars, Long Beach, Calif.; K. Rice (principal investigator) and F. Lebahn, Minneapolis; A. Fulambarker (principal investigator) and D. Ferguson, North Chicago, Ill.; P. Krumpe (principal investigator) and R. Weldermuth, Reno, Nev.; J. Liu (principal investigator) and T. Thompson, Salem, Va.; M. Habib (principal investigator) and T. Vincent, Tucson, Ariz.; S. Santiago (principal investigator), D. Boyd, and L. Robinson, West Los Angeles, Calif.; J. Sampson (principal investigator), Alexandria, La.; F. Al-Bazzaz (principal investigator), Chicago (West Side); M. Nelson (principal investigator), Kansas City, Mo.; J. McCormick (principal investigator) and S. Shariaty, Lexington, Ky.; M. Tenholder (principal investigator), Memphis, Tenn.; W. Davis (principal investigator) and Z. She, Augusta, Ga.; P. Carslis (principal investigator), Miami; B. Gray (principal investigator) and K. Laughlin, Oklahoma City; and C. Arwood (principal investigator), Pittsburgh.

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1 – Item 8

OIPE
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PATENT & TRADEMARK OFFICE

Attorney's Docket No.: 06275-150003 / D 1841-3P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.* Art Unit : 1617
Serial No. : 10/010,283 Examiner : Jennifer Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAN TROFAST, PH.D.

I, Jan Trofast, declare as follows:

1. I have been a scientist at AstraZeneca R&D (formerly Astra AB) since 1979 in the division of Medicinal Chemistry and Pharmaceutical & Analytical R&D. I received a Ph.D. in organic chemistry in 1978 from Lund Institute of Technology, Lund, Sweden. I have been studying and conducting research in the field of respiratory disorders since 1979, and I am an expert in this field. I am a co-inventor of the invention claimed in this application.

2. In collaboration with AstraZeneca, a placebo-controlled 12 month clinical trial was performed using a combination of budesonide/formoterol fumarate dihydrate (under the product name Symbicort®) in the treatment of moderate to severe COPD. Formoterol is the biologically active moiety in formoterol fumarate dihydrate (FFD). This study is published in Calverley *et al., Eur. Respir. J.* 22:912-919, 2003. In summary, before randomization, 1022 patients were treated in a 2 week initial run-in period with oral prednisolone (30 mg once daily), inhaled FFD (Oxis®; 2 puffs twice per day, each puff delivering 4.5 µg FFD to the patient from a metered dose[1] of 6.0 µg FFD), and terbutaline as needed (Bricanyl®; 0.5 mg by inhalation). The patients had the following profile:

[1] A "metered dose" is the amount of product that is positioned in the inhaler for delivery to the patient with each puff. Not all of the metered dose is delivered to the patient; some product will stick to the sides of the inhaler, or

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Age ≥ 40 years

COPD diagnosis since at least 2 years prior to the study

At least 10 pack years smoking history[2]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

All of the following medications and the placebo were delivered from a Turbuhaler® inhaler. The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/FFD combination (Symbicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide/4.5 μg FFD to the patient (corresponding to a metered dose of 200 μg budesonide and 6.0 μg FFD respectively for the monoproducts))

Group 2: Budesonide alone (Pulmicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide to the patient from a metered dose of 200 μg budesonide)

Group 3: FFD alone (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose of 6.0 μg FFD)

Group 4: Inhaled placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded.

3. The results of this study suggest that the combination of budesonide and FFD produces several synergistic effects.

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will otherwise remain in the inhaler. A "delivered dose" is the amount of product that exits the inhaler. This amount is less than the metered dose.

[2] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

For example, as shown in the graph titled "Symbicort reduces the risk of first exacerbation requiring medical intervention"[3] (Appendix 1, submitted herewith), the hazard rate was reduced (compared to placebo) by 28.5 % in patients treated with the budesonide/FFD combination. The corresponding reduction for patients treated with budesonide alone was 7.5 %, while FFD alone actually produced an increase (compared to placebo) of 1.5 %. A merely additive effect would have produced a 6.0 % reduction[4]. These data are presented in Calverley *et al.* at page 915, column 1 and in Figure 1. The data in Table 3 of Calverley *et al.* supplement these results.

4. The enclosed graph titled "Symbicort reduces the number of severe exacerbations/patient/year" (Appendix 2, submitted herewith) also strongly imply a synergistic effect of the budesonide/FFD combination therapy. As compared to treatment with placebo, treatment with FFD alone actually increased the number of exacerbations per patient per year slightly (+3%), while treatment with budesonide alone decreased the number of exacerbations per patient per year by 12%. **Patients treated with the budesonide/FFD combination, however, exhibited a 24% reduction in exacerbations.** This result demonstrates a synergistic effect, as the 24% reduction is much greater than the 9% reduction expected if the effect of the combination therapy were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002, and supplement the data presented in Calverley *et al.* at page 915, column 1.

5. A synergistic effect was also indicated in the patients' need for oral steroids during the course of the study, as shown in the graph titled "Symbicort reduces need for oral steroids"

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[3] Severe exacerbations were considered to be exacerbations requiring medical intervention, *i.e.* administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

[4] In order to assure the stability of the first order approximation used above to assess the additive effects, a fully elaborated approach is also presented. By treating these data in a multiplicative way (the model being relative), the additive effect of budesonide and formoterol is = 100 – (100-7.5)*(100+1.5)/100 = 6.1 % and the combination (Symbicort) over this is = 100 - 100*100*(100-28.5)/((100-7.5)*(100+1.5)) = 23.8 %. Note that this effect is even greater than suggested above (= 28.5-6.0 = 22.5 %), showing that calculation on the additive scale gives a conservative estimate. The same kind of multiplicatory calculations will give essentially the same result on items 4, 5, 9 and 11 below; other items below should use the additive model.

(Appendix 3, submitted herewith). Treatment with budesonide alone reduced the hazard rate of time to first oral steroid use by 14% compared to placebo, and treatment with FFD alone reduced the hazard rate by 13% as compared to placebo. **In contrast, treatment with the budesonide/FFD combination reduced the hazard rate of time to first oral steroid by 42.3% versus placebo.** This is far better than the 27% reduction that would have been expected from an additive effect of the individual budesonide and FFD components. These data supplement the data presented in Calverley *et al.* at page 915, column 1 (recalculated to placebo).

6. A synergistic effect was also indicated in the effect on night awakenings, as shown in the graph titled "Symbicort increases nights without awakenings" (Appendix 4, submitted herewith). Treatment with either budesonide alone or FFD alone resulted in an adjusted mean change in awakenings-free nights of +3.7 % (compared to placebo). If budesonide and FFD in combination had a merely additive effect on the change in awakenings-free nights, the adjusted mean change of the combination therapy (compared to placebo) would be expected to be +7.4 %. However, treatment with the combination therapy resulted in an adjusted mean change in awakenings-free nights (compared to placebo) of + 9.2 %, much greater than the calculated additive effect of 7.4 %.

7. A synergistic effect was also indicated in the morning peak expiratory flow (PEF), as shown in the graph titled "Symbicort rapidly improves and maintains morning PEF" (Appendix 5, submitted herewith). The difference in adjusted mean change of morning PEF, as compared to placebo, was 3.5 L/min for the patients treated with budesonide alone, 11.1 L/min for those treated with FFD alone, **and 18.3 L/min for the patients treated with the budesonide/FFD combination**, *i.e.*, 3.7 L/min higher than would be expected if the effect were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002, and supplement the data presented in Calverley *et al.* at page 916, Figure 3(a).

8. The graph titled "Symbicort rapidly improves and maintains evening PEF" (Appendix 6, submitted herewith) strongly imply a synergistic effect on the patients' evening

peak expiratory volume (PEF). The difference in adjusted mean change of evening PEF, as compared to the placebo, was **2.0** L/min for the patients treated with budesonide alone, **8.9** L/min for those treated with FFD alone, and **14.1 L/min for the patients treated with the budesonide/FFD combination,** *i.e.,* 3.2 L/min higher than would be expected if the effect of the budesonide/FFD combination were merely additive. These data are graphically represented in Calverley *et al.* at page 916, Figure 3(b), and recalculated to placebo for easier comparison.

9. The graph titled "Symbicort produces rapid and maintained improvement in lung function (FEV1)" (Appendix 7, submitted herewith) illustrates that FEV1 decline was less severe in patients treated with a budesonide/FFD combination therapy than in those treated with either monotherapy. The combination therapy was 14% better than placebo in this regard, while the monotherapies were respectively only **8%** and **2%** better than placebo. These data are presented in Calverley *et al.* at page 915, column 2 and in Figure 2.

10. As illustrated by the graph titled "Symbicort improves health related quality of life, HRQL" (Appendix 8, submitted herewith), the mean change in total score on St. George's Respiratory Questionnaire (SGRQ) as compared to placebo was -7.5, which was a greater improvement than that observed following treatment with budesonide alone (**-3.0**) or FFD alone (**-4.1**)[5]. These data are reported in Calverley *et al.* at page 916, column 2 and in Figure 4.

11. As illustrated by the graph titled "Symbicort reduces discontinuations compared to other treatments" (Appendix 9, submitted herewith), fewer patients withdrew from the study when they received the budesonide/FFD combination therapy than with either of the monotherapies. These data supplement the data in Table 1 of Calverley *et al.* at page 914, which reports that 71% of the patients originally enrolled in the study and who received treatment with the combination of budesonide and FFD completed the study. By comparison, only **59%** of patients receiving placebo completed the study, approximately the same as those receiving FFD alone (**56%**) or budesonide alone (**60%**). The multiple beneficial effects described above may

[5] A change of *minus* 4 points in the SGRQ represents a clinically important improvement in health related quality of life. The more negative the score, the better the quality of life.

have contributed to the fact that fewer patients receiving the budesonide/FFD combination therapy withdrew from the study. The numbers could be obtained in the graph by looking at the fraction of subjects in study at the end of the twelve month period (see also the bottom line of Table 1 at page 914 of Calverley *et al.*).

12. Taken together, the overall consistency in these variables, describing different but clinically important aspects of the disease, strongly suggests that the combination produces synergistic effects.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

By: Jan Trofast
Jan Trofast, Ph.D.

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Item 9

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Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease

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Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. P.M. Calverley, W. Boonsawat, Z. Cseke, N. Zhong, S. Peterson, H. Olsson. ©ERS Journals Ltd 2003.
ABSTRACT: Lung function in chronic obstructive pulmonary disease (COPD) can be improved acutely by oral corticosteroids and bronchodilators. Whether clinical improvement can be maintained by subsequent inhaled therapy is unknown.

COPD patients (n=1,022, mean prebronchodilator forced expiratory volume in one second (FEV1) 36% predicted) initially received formoterol (9 µg *b.i.d.*) and oral prednisolone (30 mg *o.d.*) for 2 weeks. After this time, patients were randomised to *b.i.d.* inhaled budesonide/formoterol 320/9 µg, budesonide 400 µg, formoterol 9 µg or placebo for 12 months.

Postmedication FEV1 improved by 0.21 L and health-related quality of life using the St George's Respiratory Questionnaire (SGRQ) by 4.5 units after run-in. Fewer patients receiving budesonide/formoterol withdrew from the study than those receiving budesonide, formoterol or placebo. Budesonide/formoterol patients had a prolonged time to first exacerbation (254 *versus* 96 days) and maintained higher FEV1 (99% *versus* 87% of baseline), both primary variables *versus* placebo. They had fewer exacerbations (1.38 *versus* 1.80 exacerbations per patient per year), had higher prebronchodilator peak expiratory flow, and showed clinically relevant improvements in SGRQ *versus* placebo (-7.5 units). Budesonide/formoterol was more effective than either monocomponent in both primary variables.

Budesonide/formoterol in a single inhaler (Symbicort®) maintains the benefit of treatment optimisation, stabilising lung function and delaying exacerbations more effectively than either component drug alone or placebo.
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Several randomised, controlled trials have shown that long-acting, inhaled β_2-agonists improve lung function in chronic obstructive pulmonary disease (COPD) irrespective of disease severity [1], and improve health-related quality of life (HRQL) [2, 3]. These improvements equal or exceed those seen with ipratropium [3] or theophylline [4]. Only two studies have followed the effects of treatment with long-acting, inhaled β_2-agonists over 1 yr [5, 6]. The results confirmed the effect on spirometry, but the change in HRQL was smaller than expected.

The role of inhaled corticosteroids (ICS) in COPD is more controversial. Corticosteroids do not appear to affect the rate of decline of forced expiratory volume in one second (FEV1) [7–10]. However, ICS increased postbronchodilator FEV1 in two studies [8, 9], and reduced the severity [11] and frequency of exacerbations when this end-point could be reliably assessed [9]. These observations have led to ICS being recommended for COPD patients with FEV1 <50% predicted who show a spirometric response [12]. In two 1-yr studies, the clinical effect of ICS on exacerbations requiring oral steroids was confirmed [5, 6]; the reduction in exacerbation frequency was less evident for patients taking ICS alone in the study by SZAFRANSKI *et al.* [5]. These results may suggest that sicker patients require more than just ICS in their treatment for COPD.

For editorial comments see page 874.

Combining a long-acting β_2-agonist and an ICS as maintenance therapy has been very successful in managing bronchial asthma [13, 14], but less is known about this treatment strategy in COPD. Lung function (prebronchodilator FEV1) is improved when these drugs are combined, compared with monotherapy [15], and recent studies have found that combining therapies is also associated with fewer exacerbations and improved HRQL, compared with placebo treatment [5, 6].

Patients with more severe COPD (Global Initiative for Obstructive Lung Disease (GOLD) stages III and IV) frequently experience exacerbations, which impact on their HRQL [16]. Prolonging the time to exacerbation may delay the deterioration of the disease and help maintain health status, an important aim in the treatment of COPD. Moreover, it can be difficult to separate the improvement in health status that occurs at the start of a clinical trial, due to closer medical attention, from the effects of treatment itself, and this caveat can reduce the power of the study to assess the true therapeutic effect on this outcome. To address this difficulty, a clinical trial was conducted in which inhaled formoterol and oral corticosteroids were administered during a short run-in period, to ensure that patients' treatment was optimised before entry into the trial. During the 12-month, randomised treatment period in patients with COPD, an ICS (budesonide) and a long-acting β_2-agonist (formoterol) given in the same inhaler were compared with the component drugs given

separately and with placebo. The primary outcomes were time to first exacerbation and change in FEV1. Data were also recorded on HRQL, peak expiratory flow (PEF), symptoms, use of reliever medication and adverse events (AEs). This protocol allowed the authors to test a clinically relevant situation, namely whether the short-term improvement that follows a period of treatment optimisation can be maintained over a longer time by inhaled therapy, and to investigate which drugs change what aspect of patient well-being.

Methods

Patients

Outpatients with COPD (GOLD stages III and IV) [12] were recruited based on the following criteria: aged ≥40 yrs, COPD symptoms for >2 yrs, smoking history of ≥10 pack-yrs, FEV1/vital capacity (VC) ≤70% prebronchodilator, FEV1 ≤50% of predicted normal value prebronchodilator, using inhaled bronchodilators as reliever medication, ≥1 COPD exacerbation requiring a course of oral corticosteroids and/or antibiotics 2–12 months before the first clinic visit.

Principal exclusion criteria were: a history of asthma/seasonal allergic rhinitis before the age of 40 yrs, any relevant cardiovascular disorders or significant disease/disorder, which may have put patients at risk or influenced the results of the study, an exacerbation of COPD requiring medical intervention within 4 weeks prior to enrolment and/or during run-in, use of oxygen therapy, β-blocking agents or nonallowed medications. All patients gave written, informed consent and the study was approved by an Ethics Committee for each centre.

Study design

This was a randomised, double-blind, placebo-controlled, parallel-group study involving 109 centres in 15 countries or regions. All medication was from AstraZeneca, Lund, Sweden, and delivered *via* a dry powder inhaler (Turbuhaler®; AstraZeneca). During the 2-week run-in, patients received oral prednisolone (30 mg) *o.d.* and inhaled formoterol (Oxis®) 2×4.5 µg *b.i.d.*, and terbutaline (Bricanyl®) 0.5 mg as needed. Patients were then randomised to 12 months of treatment with either budesonide (Pulmicort®) 2×200 µg *b.i.d.*, formoterol 2×4.5 µg *b.i.d.*, budesonide/formoterol (Symbicort®; this Turbuhaler® delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler® monoproducts) 2×160/4.5 µg *b.i.d.*, or placebo (lactose monohydrate) *b.i.d* with terbutaline 0.5 mg as needed.

Certain medications were allowed, with restrictions, after randomisation. Courses of oral corticosteroids (maximum 3 weeks per course) and antibiotics were allowed in the event of exacerbations. Parenteral steroids and/or nebulised treatment (single injections/inhalations) were allowed at emergency visits.

The following medications were disallowed from recruitment: inhaled steroids (except the study medication), disodium cromoglycate, leukotriene antagonists or 5-lipoxygenase (5-LO) inhibitors, bronchodilators (other than study medication and terbutaline 0.5 mg (Bricanyl®) as needed), antihistamines, any medication containing ephedrine, and β-blockers, including eye-drops.

The following medications were withheld prior to recruitment: short-acting inhaled or oral β_2-agonists (6 h before), inhaled or oral long-acting β_2-agonists (48 h), inhaled short-acting anticholinergics (8 h), inhaled long-acting anticholinergics (7 days), xanthine-containing derivatives *o.d.* (48 h), xanthine-containing derivatives *b.i.d.* (24 h), leukotriene antagonists or 5-LO inhibitors (48 h).

Assessments

Patients attended the clinics at recruitment, randomisation and after 1, 2, 3, 6, 9 and 12 months of treatment. The primary variables were time to first exacerbation and change in post-medication FEV1. The secondary variables were number of exacerbations, time to and number of oral corticosteroid-treated episodes, morning and evening PEF, slow VC, HRQL, symptoms, use of reliever medication and AEs.

Exacerbations requiring medical intervention (oral antibiotics and/or corticosteroids or hospitalisation) were recorded at each visit after randomisation. The time to and number of exacerbations and oral corticosteroid-treated episodes were analysed.

Predicted FEV1 was calculated at recruitment using European Respiratory Society (ERS) equations [17]. FEV1 was measured before and 15 min after two inhalations of terbutaline 0.5 mg and the per cent increase from baseline in FEV1 was calculated. Spirometry (FEV1 and slow VC) measured after study medication and at least 6 h postreliever, at each clinic visit, met ERS standards [17]. Wherever possible, spirometry was performed at the same time of day, using the same spirometer (calibrated on each study day in accordance with the trademark specification), and supervised by the same well-trained study staff. Patients were instructed to rest for 15 min before measurement and spirometry was performed in a sitting position whilst wearing a noseclip. All spirometers met or exceeded the American Thoracic Society recommendations.

Prebronchodilator PEF, measured using a Mini-Wright® peak flow meter (Clement Clark, Harlow, UK), was recorded daily in a diary, in the morning and evening as the best of three attempts before inhalation of the study medication.

The St George's Respiratory Questionnaire (SGRQ) [18] was used to assess HRQL. Questionnaires were completed at recruitment, at randomisation, and at 6 and 12 months; a Total score was calculated. A lower score indicates better health, while a change of ≥4 units indicates the minimal clinically important difference relevant to the patient [19]. Symptoms of shortness of breath, cough, chest tightness and night-time awakenings (on a 5-point scale from 0 (none, unaware of symptoms) to 4 (severe)), as well as use of reliever medication, were recorded daily in a patient diary. AEs were monitored at each postrandomisation visit by asking a standard question.

Analysis

With 150 patients per group, a difference in survival curves could be detected with 80% power if 66% exacerbated in the reference group and 50% in the comparative group. Adjusting for a 35% dropout rate implied ~230 patients per group.

An intention-to-treat analysis was used and all hypothesis testing was with two-sided alternative hypotheses; $p<0.05$ was considered statistically significant. Time to first exacerbation was analysed using a log-rank test and described further by hazard rates from a Cox proportional hazards model, with treatment as factor and stratifying by country. The number of exacerbations was analysed using a Poisson regression model (expressed as mean rate *i.e.* mean number of exacerbations per patient per year). Treatment and country were used as factors, time in study as an offset variable, and confidence intervals were adjusted for overdispersion. Oral corticosteroid

courses were analysed similarly to exacerbations. The FEV1 and VC end-points were the mean of all available measurements during the treatment period, analysed in a multiplicative analysis of variance (with logarithm of values) with treatment and country as factors, and the randomisation value as a covariate. The mean ratios were presented as per cent increases. Both primary variables were required to give statistical significance at the 5% level in order to keep the overall significance level to 5% in the final conclusion [20]. Differences in subgroup response were addressed using standard "treatment by subgroup" interaction analyses. SGRQ was analysed in a similar manner to FEV1 but based on the last available measurement on treatment. Diary-card variables were also analysed in a similar manner to FEV1 but with an additive model.

Results

Patients

Of 1,141 patients enrolled into the study, 119 (10%) withdrew during run-in; 26% of these were due to COPD worsening and 24% due to AEs other than COPD worsening. Following run-in, 1,022 patients were randomised, of whom 629 (62%) completed the study (table 1). Mean demographic and baseline characteristics were similar across all treatment groups (table 2) and correspond in general to GOLD stages III and IV COPD [12]. After the initial period of treatment optimisation, the group mean FEV1 had increased by (mean±SD) 0.21±0.32 L and the SGRQ Total score decreased by 4.5±10.7 units.

Withdrawal from study

The budesonide/formoterol group had a lower risk of withdrawing from the study compared with the placebo, budesonide and formoterol groups (table 1). There was no significant difference in withdrawal rates *versus* placebo in either the budesonide group or the formoterol group.

After randomisation, 393 patients withdrew from the study; 193 of these were due to COPD worsening, 72 withdrew because of AEs other than COPD worsening, and 128 for other reasons (table 1). Significantly fewer withdrawals due to COPD worsening were reported in the budesonide/formoterol

Table 1. – Patient flow and withdrawals

	B/F	B	F	Placebo	Total
Patients enrolled					1141
Patients withdrawn during run-in					119
Patients randomised	254	257	255	256	1022
Patients withdrawn after randomisation#	74 (29)	102 (40)	111 (44)	106 (41)	393 (38)
Patients withdrawn due to COPD worsening¶	28 (11)	46 (18)	59 (23)	60 (23)	193 (19)
Patients withdrawn due to adverse event other than COPD worsening	20 (8)	21 (8)	20 (8)	11 (4)	72 (7)
Patients lost to follow-up	0 (0)	2 (0.8)	3 (1.2)	3 (1.2)	8 (0.8)
Eligibility criteria not fulfilled	4 (1.6)	4 (1.6)	4 (1.6)	6 (2.3)	18 (1.8)
Other reasons	22 (8.7)	29 (11.3)	25 (9.8)	26 (10.2)	102 (10.0)
Patients completing study	180 (71)	155 (60)	144 (56)	150 (59)	629 (62)

Data are presented as n (% of randomised patients per group) unless otherwise stated. B: budesonide; F: formoterol; COPD: chronic obstructive pulmonary disease. #: p=0.001 budesonide/formoterol *versus* placebo, p=0.037 budesonide/formoterol *versus* budesonide, p<0.001 budesonide/formoterol *versus* formoterol, p=0.223 budesonide *versus* placebo, p=0.950 formoterol *versus* placebo (Cox proportional hazards model); ¶: p<0.001 budesonide/formoterol *versus* placebo and *versus* formoterol, p=0.038 budesonide/formoterol *versus* budesonide, p=0.031 budesonide *versus* placebo, p=0.616 formoterol *versus* placebo (Cox proportional hazards model).

Table 2. – Patient demographic and baseline characteristics (at enrolment, unless otherwise stated)

	B/F	B	F	Placebo
Patients randomised n	254	257	255	256
Male %	78	74	75	75
Age yrs	64 (42–86)	64 (41–85)	63 (41–84)	65 (43–85)
Current smokers %	33	39	36	30
Pack-yrs	39 (10–240)	39 (10–150)	38 (10–120)	39 (10–150)
Previous medication % of patients				
ICS	47	51	48	46
Inhaled SABAs	52	49	53	48
Anticholinergics	29	30	30	32
Inhaled LABAs	31	30	30	25
Xanthines	37	33	40	36
Inhaled combination of β_2-agonist and anticholinergic	16	18	18	22
FEV1 L	0.98±0.33	0.99±0.33	1.00±0.32	0.98±0.33
FEV1 % predicted	36±10	36±10	36±10	36±10
FEV1/VC %	42±12	44±12	44±12	44±11
Reversibility % predicted	6±7	6±7	6±6	6±6
Baseline SGRQ Total score at randomisation	48±19	49±18	47±19	48±18

Data are presented as mean (range) or mean±SD unless otherwise stated. B: budesonide; F: formoterol; ICS: inhaled corticosteroid; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; FEV1: forced expiratory volume in one second; VC: vital capacity; SGRQ: St George's Respiratory Questionnaire.

group compared with the placebo, budesonide and formoterol groups (table 1).

Exacerbations

Budesonide/formoterol prolonged time to first exacerbation compared with all other treatments (all p<0.05, log-rank test; fig. 1). Hazard rate analysis showed that the risk of having an exacerbation while being treated with budesonide/formoterol was reduced by 22.7%, 29.5% and 28.5% *versus* budesonide, formoterol and placebo, respectively. The exacerbation rate with budesonide/formoterol was reduced compared with placebo (23.6%) and formoterol (25.5%) but not with budesonide alone (13.6%) (table 3). Neither budesonide nor formoterol affected either measure of exacerbation compared with placebo.

When the analysis was restricted to oral corticosteroids given due to exacerbations, the lowest rates were found in the budesonide/formoterol and budesonide treatment groups (table 3). Budesonide/formoterol prolonged the time to first course of oral corticosteroids after randomisation; risk reductions were 32.7% and 33.8% *versus* budesonide and formoterol, respectively (both p<0.01), and 42.3% *versus* placebo (p<0.001). Budesonide/formoterol also reduced the rate of oral corticosteroid courses by 28.2%, 30.5% and 44.7% *versus* budesonide, formoterol and placebo, respectively; budesonide alone reduced the number of oral corticosteroid courses compared with placebo but formoterol did not (table 3).

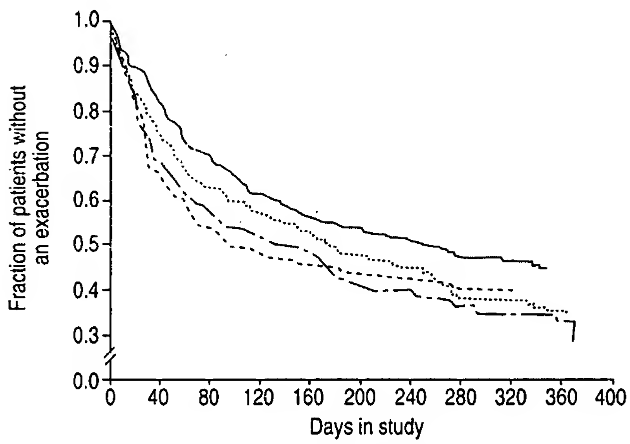

Fig. 1.–Kaplan-Meier plot of time to first exacerbation by treatment group. Log-rank tests of budesonide/formoterol (——) *versus* budesonide (··········), p=0.037; budesonide/formoterol *versus* formoterol (— -), p=0.002; budesonide *versus* placebo (- - -), p=0.796; formoterol *versus* placebo, p=0.490; and budesonide/formoterol *versus* placebo, p<0.05.

Lung function

After the optimisation period, the improvement in FEV1 seen during run-in was maintained with budesonide/formoterol treatment throughout the study. In contrast, FEV1 declined greatly and rapidly with all other treatments. This difference was significant with budesonide/formoterol compared with placebo (14%), budesonide (11%) and formoterol (5%), and with formoterol *versus* placebo (8%), but not with budesonide *versus* placebo (2%) (fig. 2).

Changes in VC closely followed those of FEV1. Budesonide/formoterol and formoterol improved VC *versus* placebo (both p<0.001), while budesonide/formoterol also improved VC *versus* budesonide (p<0.001). Budesonide/formoterol therapy was also associated with higher morning PEF compared with all other treatments, and higher evening PEF compared with placebo and budesonide (fig. 3).

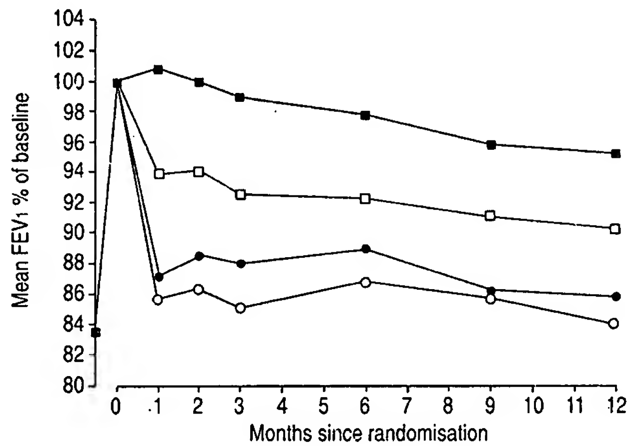

Fig. 2.–Changes in mean forced expiratory volume in one second (FEV1) in the four treatment groups from randomisation to the average of all available measurements during the 12-month treatment period. Budesonide/formoterol (■) *versus* budesonide (●), p<0.001; budesonide/formoterol *versus* formoterol (□), p=0.002; budesonide *versus* placebo (○), p=0.145; formoterol *versus* placebo, p<0.001; budesonide/formoterol *versus* placebo, p<0.001.

Table 3.–Analysis of exacerbations and oral corticosteroid courses due to exacerbations

	B/F	B	F	Placebo
Time to first exacerbation				
Median number of days	254	178	154	96
#RR (95% CI) B/F *versus* other groups+		0.773 (0.611–0.980)*	0.705 (0.558–0.891)**	0.715 (0.562–0.910)
p-value¶	0.006	0.512	0.901	
Total number of exacerbations				
Mean rate per patient per year	1.38	1.60	1.85	1.80
RR (95% CI) B/F *versus* other groups+		0.864 (0.679–1.100)	0.745 (0.587–0.945)*	0.764 (0.600–0.973)
p-value¶	0.029	0.308	0.828	
Exacerbations requiring oral corticosteroids				
Mean rate per patient per year	0.63	0.87	0.91	1.14
RR (95% CI) B/F *versus* other groups+		0.718 (0.543–0.949)*	0.695 (0.523–0.923)*	0.553 (0.420–0.728)
p-value¶	<0.001	0.044	0.085	

B: budesonide; F: formoterol; RR: rate ratio; CI: confidence interval. #: a RR of 0.715 represents a reduction in rate of 28.5%; ¶: *versus* placebo; +: rates from Poisson regression model, RR is hazard ratio from Cox proportional hazards model. *: p<0.05 in favour of budesonide/formoterol; **: p<0.01 in favour of budesonide/formoterol.

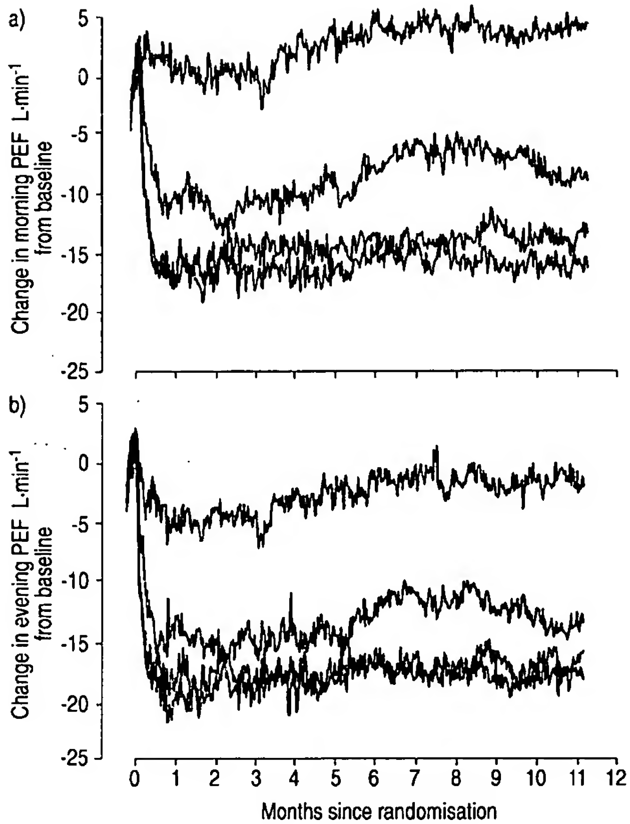

Fig. 3.–Change in peak expiratory flow (PEF) from randomisation to the average of all available measurements during the 12-month treatment period (from daily diary-card data). Budesonide/formoterol (top line) therapy was associated with a) higher morning PEF *versus* placebo (bottom line; 18 $L \cdot min^{-1}$ difference, $p<0.001$), budesonide (line third from top; 15 $L \cdot min^{-1}$, $p<0.001$) and formoterol (line second from top; 7 $L \cdot min^{-1}$, $p=0.007$). Formoterol *versus* placebo $p<0.001$. b) Budesonide/formoterol therapy was associated with higher evening PEF *versus* placebo (14 $L \cdot min^{-1}$, $p<0.001$) and budesonide (12 $L \cdot min^{-1}$, $p<0.001$), but not *versus* formoterol (5 $L \cdot min^{-1}$) and this improvement was sustained throughout the treatment phase. Formoterol was also associated with placebo ($p<0.001$).

For both exacerbations and FEV1, interaction analyses between treatment and sex, smoking status/history, reversibility or use of ICS at entry, were performed in order to investigate differences in treatment response. There was no evidence of heterogeneity in the treatment differences with respect to the primary variables in any of these categories, *i.e.* the results in these groups were consistent with the main analysis.

Health-related quality of life

Baseline values for the SGRQ Total score were similar in each group and high, indicating poor HRQL (table 2). At the end of the run-in period, Total scores had improved by a mean of 4.5 units (range 3.6–4.8; fig. 4). During the treatment period, the Total scores fell further in the budesonide/formoterol group, representing an additional improvement beyond that achieved during run-in. Treatment with budesonide or formoterol allowed the initial improvement in HRQL to be maintained, while HRQL in the placebo group deteriorated to the original (prerun-in) values (fig. 4). Thus,

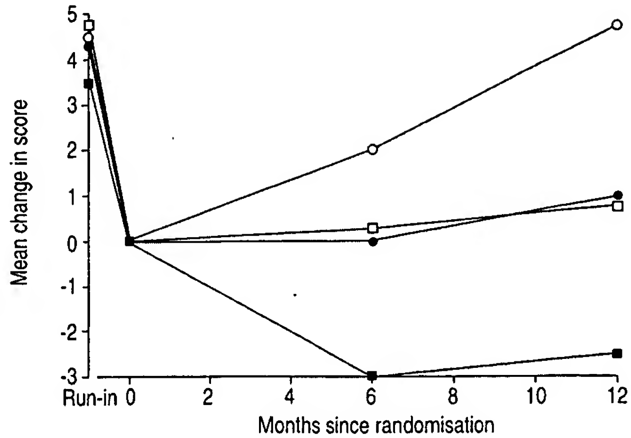

Fig. 4.–Time course of the change in St George's Respiratory Questionnaire Total scores relative to first attendance measured at clinic visits. At 12 months, budesonide/formoterol (■) *versus* budesonide (●), $p=0.001$; budesonide/formoterol *versus* formoterol (□), $p=0.014$; budesonide *versus* placebo (○), $p<0.05$; formoterol *versus* placebo, $p<0.01$; and budesonide/formoterol *versus* placebo, $p<0.001$.

all active treatments improved the Total score *versus* placebo, with the greatest improvement occurring with budesonide/formoterol (differences at 12 months of -7.5, -3.0 and -4.1 *versus* placebo for budesonide/formoterol, budesonide and formoterol, respectively). Similarly, Symptoms, Activity and Impacts domain scores were each improved by ⩾5.5 units in those patients receiving budesonide/formoterol compared with the placebo group ($p<0.01$). In addition, budesonide/formoterol showed improvements *versus* monocomponents in the Activity (changes of -3.6 *versus* budesonide and -3.5 *versus* formoterol, both $p<0.05$) and Impacts (changes of -5.7 ($p<0.001$) *versus* budesonide, and -3.7 ($p<0.05$) *versus* formoterol) domains, but not in the Symptoms domain (-2.8 *versus* budesonide and -0.6 *versus* formoterol).

Symptoms

Budesonide/formoterol and formoterol improved the total symptom score and the individual symptom scores for shortness of breath, chest tightness and night-time awakenings compared with placebo. Budesonide also improved the night-time awakenings score compared with placebo. None of the treatments significantly improved the cough score. Mean data for changes from run-in to end of treatment in symptom scores and differences between groups are shown in table 4.

Use of reliever medication

Budesonide/formoterol significantly reduced the use of reliever medication by 0.8 inhalations per day *versus* both budesonide and placebo (both $p<0.001$), and by 0.3 inhalations per day *versus* formoterol ($p<0.05$), and formoterol reduced reliever medication intake by 0.4 inhalations per day *versus* placebo ($p<0.01$). Budesonide alone had no effect on this variable compared with placebo.

Safety

No further safety issues for budesonide/formoterol were identified in this study compared with what is previously

Table 4. – Mean changes from run-in to end of treatment in symptom scores

	Total symptom score (0–16)	Shortness of breath score (0–4)	Chest tightness score (0–4)	Cough score (0–4)	Night-time awakening score (0–4)
B/F *versus* placebo	-0.56 (-0.89–-0.24)	-0.21 (-0.32–-0.10)	-0.16 (-0.26–-0.05)	-0.07 (-0.17–0.03)	-0.16 (-0.27–-0.05)
p-value	<0.001	<0.001	0.004	0.180	0.004
B/F *versus* B	-0.26 (-0.58–-0.07)	-0.12 (-0.23–-0.01)	-0.09 (-0.20–0.01)	-0.02 (-0.12–0.08)	-0.05 (-0.16–0.06)
p-value	0.120	0.040	0.080	0.651	0.361
B/F *versus* F	-0.02 (-0.35–0.30)	0.00 (-0.11–0.11)	-0.01 (-0.12–0.09)	-0.02 (-0.12–0.08)	-0.04 (-0.15–0.07)
p-value	0.891	0.946	0.788	0.705	0.463
B *versus* placebo	-0.30 (-0.63–0.02)	-0.09 (-0.20–0.02)	-0.06 (-0.17–0.04)	-0.05 (-0.15–0.05)	-0.11 (-0.21–-0.00)
p-value	0.067	0.100	0.238	0.372	0.049
F *versus* placebo	-0.54 (-0.87–-0.21)	-0.21 (-0.32–-0.10)	-0.14 (-0.25–-0.04)	-0.05 (-0.15–0.05)	-0.12 (-0.22–-0.01)
p-value	0.001	<0.001	0.008	0.335	0.033

Data are presented as mean (95% confidence interval) unless otherwise stated. B: budesonide; F: formoterol.

known for budesonide/formoterol, budesonide and formoterol in COPD and asthma. The mean number of AEs experienced with budesonide/formoterol was no different from that with placebo (5, 5, 6 and 5 AEs per 1,000 treatment days for the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively), and the most frequently reported AEs were similar across the treatment groups (table 5). The lowest number of withdrawals was in the budesonide/formoterol group (table 1) and the lowest number of serious AEs other than deaths were in the budesonide/formoterol and placebo groups (65, 88, 85 and 66 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively). The number of serious AEs related to COPD was 40, 40, 55 and 38 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively. The numbers of deaths were 5, 6, 13 and 5 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively. Most of the deaths were events related to COPD and only a few were related to cardiovascular events.

Discussion

Many clinicians manage newly referred COPD patients by intensifying their treatment, often including a period of oral corticosteroid therapy with the hope of selecting individuals who are "corticosteroid responders". A substantial number of patients show spirometric improvements with either a β_2-agonist or oral corticosteroids, or both [21]. Unfortunately, neither the presence of a "positive" or "negative" oral corticosteroid response in patients with more severe COPD predicts future response to inhaled therapy [9]. Whether these improvements in lung function are accompanied by changes in symptomatic end-points like HRQL has not been studied, nor has the ability of inhaled drugs to maintain these effects been assessed, although results from observational studies suggest that at least ICS may be beneficial [22]. This study shows that significant short-term improvements in lung function (both FEV1 and PEF) and HRQL occur after optimised treatment with formoterol and oral corticosteroids, and that these improvements can be maintained for a year using budesonide and formoterol in the same inhaler.

Table 5. – The most frequently reported adverse events (AEs)

	B/F	B	F	Placebo
Subjects n	254	257	255	256
COPD#	48 (19)	62 (24)	73 (29)	79 (31)
Respiratory infection	36 (14)	34 (13)	33 (13)	24 (9)
Fever	5 (2)	9 (4)	11 (4)	2 (1)
Dyspnoea	5 (2)	5 (2)	12 (5)	5 (2)
Back pain	8 (3)	4 (2)	6 (2)	7 (3)
Pharyngitis	7 (3)	5 (2)	8 (3)	5 (2)
Chest pain	8 (3)	4 (2)	6 (2)	5 (2)
Hypertension	6 (2)	9 (4)	3 (1)	5 (2)
Pneumonia	8 (3)	5 (2)	7 (3)	2 (1)
Rhinitis	11 (4)	3 (1)	6 (2)	1 (<0.5)
Dysphonia	5 (2)	5 (2)	1 (<0.5)	1 (<0.5)
Moniliasis	4 (2)	4 (2)	2 (1)	0 (0)

Data are presented as n (%) of patients reporting at least one AE after the first dose of investigational product unless otherwise stated. B: budesonide; F: formoterol; COPD: chronic obstructive pulmonary disease. #: COPD was reported as an AE only if the COPD symptom (bronchitis, phlegm, cough, increased sputum production, breathlessness, wheeze, dyspnoea) was serious (resulted in death, was life-threatening, required hospitalisation or prolonged existing hospitalisation, or resulted in persistent or significant disability/incapacity), or resulted in the patient's withdrawal from the study.

This is the first study to show that after an intensification regimen, administration of an ICS and long-acting β_2-agonist in a single inhaler prolongs the time to a first COPD exacerbation, compared with monocomponents. Moreover, these data add further strong support to recent studies where these drug treatment classes have been combined and therapy has initially been withdrawn, rather than optimised, during the run-in phase [5, 6]. The exacerbation frequency in this study was almost identical to that reported in the previous study of budesonide/formoterol in COPD patients of a similar disease severity [5], and the effects of each treatment were the same in both studies. In this study, budesonide/formoterol was clearly better than monocomponents at preventing exacerbations, while budesonide had a small effect on episodes where oral corticosteroids were considered necessary. The lack of effect of formoterol may reflect the more severe nature of the episodes used as the outcome here (*i.e.* requiring medical intervention) rather than the "bad days" used as a surrogate for exacerbations in other studies [3]. The similarities of the data presented in this paper to those of SZAFRANSKI *et al.* [5] indicate that prior treatment optimisation does not influence this outcome. The more severe disease in the patients studied (FEV1 36% pred) is the likely explanation of the greater number of episodes seen here compared with other studies [6, 9], a difference that increases the power of the study to detect an effect of treatment. The 24% reduction in exacerbations with budesonide/formoterol compared with placebo may translate into worthwhile improvements in patient well-being. Furthermore, the reductions are probably underestimated since the lowest withdrawal rate occurred in the budesonide/formoterol group. It is likely that the most severely ill patients dropped out first, potentially leading to a lower number of exacerbations in the other groups. To some extent, this bias applies to lung function and HRQL differences as well.

Budesonide/formoterol was able to maintain FEV1 at the run-in level over the study year. In contrast, lung function (both FEV1 and PEF) returned to baseline by 1 month in patients treated with either placebo or budesonide and, as judged by the PEF data from the daily diary cards, this change occurred within 2 weeks of randomisation to these treatments. Numerically, the formoterol data lay between those of the other treatment limbs, but the values were significantly smaller than those measured using budesonide/formoterol. The size of the spirometric changes, comparing budesonide/formoterol with placebo and individual components, was almost identical to that seen when combination therapy was introduced after a period of treatment withdrawal [5, 6], rather than after the intensification regimen used here. The PEF data also show that within 2 weeks of stopping intensified therapy, clinical benefits of treatment optimisation were diminished in all patients not taking budesonide/formoterol.

Budesonide/formoterol produced significant improvements in daily symptom scores compared with placebo, as did formoterol *versus* placebo (except for cough, which was unchanged). The absolute changes were similar to those seen by SZAFRANSKI *et al.* [5] who used the same questionnaire. Even modest improvements in symptom scores are likely to lead to improved mobility and an increased level of activity. However, there were statistically and clinically significant differences between treatments in their ability to sustain the HRQL improvement after optimisation of therapy. Budesonide/formoterol treatment was associated with the largest difference in the SGRQ Total score compared with placebo, which clearly exceeded the minimum clinically important difference of 4 units [19]. Improvements in Total score compared with placebo were also clinically important with formoterol alone, and approached clinical relevance for budesonide alone. The additional effect of budesonide/formoterol on HRQL compared with monocomponents is likely to reflect the lower number of exacerbations experienced by these patients, since HRQL is known to be worse in frequent exacerbators [16].

All the active treatments had some positive effect on HRQL; the change seen over the year in the budesonide group being almost identical to that seen in the less spirometrically impaired Inhaled Steroids in Obstructive Lung Disease study patients, who were also studied after an initial course of prednisolone [9]. Inclusion of an optimised treatment phase may overcome problems in assessing HRQL in clinical studies as it reduces the immediate effect of withdrawing ICS that has been associated with more frequent exacerbations [23, 24]. This approach should permit a more realistic comparison to be made of treatment effect on HRQL and overcomes the "clinical-trial effect" seen in the placebo limb of other 1-yr trials [6].

In this study, AEs were monitored by specific enquiry at each visit. No new safety issues related to treatment with budesonide/formoterol were identified during 12-months treatment. The incidence of AEs related to COPD was clearly lower in the budesonide/formoterol group compared with the other groups, and overall, a low incidence of hoarseness and moniliasis was reported.

This study did not collect bone mineral density data, although the dose of budesonide used did not affect this variable during 3 yrs of treatment in patients with less advanced COPD [25]. As expected when studying a COPD population of this severity, a number of deaths occurred. The number of serious AEs and deaths reported were highest in the formoterol treatment group and most of these were events related to COPD. An investigation into the individual causes of death did not give an explanation for the apparent difference between the groups, and no increase in mortality during formoterol treatment without ICS was observed in a previous study with a similar patient population [5]. Conversely, increased disease severity/mortality has been reported in some recently published studies with bronchodilators alone [26–28]. These observations, together with the potential seriousness of severe exacerbations, suggest that a combination of a long-acting bronchodilator and an ICS may be particularly appropriate in patients with this severity of COPD.

The reasons for the improved efficacy of budesonide/formoterol are not yet clear, although corticosteroids can upregulate the number of β_2-receptors on the cell membrane and β_2-agonists may increase the nuclear localisation of glucocorticoid receptors [29]. It also seems that formoterol and budesonide in combination are more effective at reducing proliferation of airway smooth muscle than either drug alone, as a result of synchronised cellular signalling [30]. Clinically, each type of drug appears to add something to the combined effect with the improvement in symptoms, lung function (FEV1, PEF), and HRQL associated with formoterol being complemented by the reduction in exacerbations and better HRQL seen with budesonide. Whether these effects are merely additive or represent true synergy cannot be established here, but the difference in treatment withdrawal between the group taking budesonide/formoterol and those taking the other treatments is likely to be explained by these multiple beneficial actions.

This study has a number of implications. It provides further and clearer evidence of the effectiveness of ICS and long-acting β_2-agonists on health status, exacerbations, lung function (FEV1 and PEF) and HRQL, in COPD (GOLD stages III and IIV), and of their additional clinical benefit when combined in a single inhaler. Secondly, standardising therapy for a period before entry into a long clinical trial allowed greater improvements in HRQL than seen in similar trials that did not include this run-in treatment. This is a novel approach that may allow for easier interpretation of this end-point, and merits further study.

Finally, this study provides evidence that intensifying treatment in stable chronic obstructive pulmonary disease may be a useful way of rapidly improving patient well-being and that this approach merits future study as an alternative to stepwise increments in treatment intensity.

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Item 10

Articles

Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial

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Summary

Background Little is known about the long-term efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease (COPD). We investigated the efficacy of inhaled budesonide on decline in lung function and respiratory symptoms in a 3-year placebo-controlled study of patients with COPD.

Methods We used a parallel-group, randomised, double-blind, placebo-controlled design in a single-centre study, nested in a continuing epidemiological survey (the Copenhagen City Heart Study). Inclusion criteria were as follows: no asthma; a ratio of forced expiratory volume in 1 s (FEV_1) and vital capacity of 0·7 or less; FEV_1 which showed no response (<15% change) to 1 mg inhaled terbutaline or prednisolone 37·5 mg orally once daily for 10 days. 290 patients were randomly assigned budesonide, 800 μg plus 400 μg daily for 6 months followed by 400 μg twice daily for 30 months, or placebo for 36 months. The mean age of the participants was 59 years and the mean FEV_1 2·37 L or 86% of predicted. The main outcome measure was rate of FEV_1 decline. Analyses were by intention to treat.

Findings The crude rates of FEV_1 decline were slightly smaller than expected (placebo group 41·8 mL per year, budesonide group 45·1 mL per year). The estimated rates of decline from the regression model did not differ significantly (49·1 mL *vs* 46·0 mL per year; difference 3·1 mL per year [95% CI −12·8 to 19·0]; p=0·7). Before the study, the minimum relevant difference was defined as 20 mL per year; this difference was outside the 95% CI. No effect of inhaled budesonide was seen on respiratory symptoms. 316 exacerbations occurred during the study period, 155 in the budesonide group and 161 in the placebo group. Treatment was well tolerated.

Interpretation Inhaled budesonide was of no clinical benefit in COPD patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD.

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Introduction

Although the use of inhaled corticosteroids in asthma is regarded as first-line therapy, treatment with inhaled corticosteroids in chronic obstructive pulmonary disease (COPD) is not based on evidence. Nevertheless, inhaled corticosteroids are used extensively in COPD; for example, in a Canadian survey 43% of patients who used inhaled corticosteroids had COPD.[1] Although inhaled corticosteroids can reduce cough and mucus secretion by suppressing acute inflammatory changes in the airways, the long-term aim is directed towards decreasing the excess decline in forced expiratory volume in 1 s (FEV_1), which is characteristic of COPD.

Data on the effect of inhaled corticosteroids on rate of FEV_1 decline are limited and leave much room for different interpretations owing to below optimum methods. An early indication of a beneficial effect of corticosteroids has come from uncontrolled studies of long-term treatment with low to moderate doses of systemic corticosteroids.[2,3] However, there have been no placebo-controlled long-term studies of oral corticosteroids and few controlled long-term studies of inhaled corticosteroids in COPD. Kerstjens and colleagues[4] showed an effect on both FEV_1 and number of exacerbations, but their study had limited value because no distinction was made between asthma and COPD at inclusion. This distinction was more obvious in a smaller study,[5] which also showed an effect of inhaled corticosteroids of FEV_1. Two studies[6,7] have reported substantial effects on the rate of FEV_1 decline, although the statistical power was poorly described. A meta-analysis of substrata including patients without asthmatic features from three of these studies[4-6] showed an estimated 2-year difference in prebronchodilator FEV_1 between patients treated with inhaled corticosteroids and placebo (34 mL per year).[8] This difference was significant even though a third of the patients originally included were excluded from the meta-analysis. Paggiaro and colleagues[9] showed an effect of inhaled fluticasone on FEV_1, respiratory symptoms, and disease severity in patients with well-defined COPD; the study, however, only lasted 6 months.

The aim of this study was to assess the long-term efficacy of inhaled budesonide on change in FEV_1 in individuals with airway obstruction in whom FEV_1 was not substantially improved in response to inhaled β_2-agonists and oral steroids. Respiratory symptoms and frequency of exacerbations were secondary outcome measures.

Methods

Study population

The study was a 3-year double-blind, parallel-group, randomised clinical trial nested in a continuing epidemiological study, the Copenhagen City Heart Study (CCHS). The CCHS was started in the mid-1970s and the study population was a random, age-stratified sample of 19 327 individuals of 87 172 aged at least

20 years, who were living in a defined area around Rigshospitalet in Copenhagen in 1976. In 1976–78, CCHS examined 14 223 individuals (response rate 73·6%); a detailed description of the study procedure has been published previously.[10,11] The study population has been re-examined and new participants in the youngest age-group have been added to the study after 5 years and 15 years. At the latest survey in 1992–94, 10 127 individuals were questioned about respiratory symptoms and examined by spirometry (Vitalograph, Ennis, Ireland). Individuals with an FEV_1/vital capacity ratio of 0·7 or less and no self-reported asthma were referred to this study for further screening for inclusion.

Inclusion criteria were as follows: CCHS participant; age 30–70 years; FEV_1/vital capacity ratio 0·7 or less; FEV_1 reversibility after inhalation of 1·0 mg terbutaline from Turbuhaler (Bricanyl, Lund, Sweden) of less than 15% of prebronchodilator FEV_1; FEV_1 reversibility after 10 days of treatment with oral prednisolone 37·5 mg daily of less than 15% of prebronchodilator FEV_1; and informed consent. Pack-years or other measures of cigarette smoking were not part of inclusion criteria. The main exclusion criterion was long-term treatment (more than two episodes of more than 4 weeks) with oral or inhaled steroids within 6 months of study entry. Other exclusion criteria were pregnancy or lactation, intention to become pregnant, other serious systemic disease that could influence the results of this study (investigators' judgment), chronic alcohol or drug use, and participation in other clinical studies of COPD within 1 month of inclusion.

Design and procedures

When patients were referred from CCHS, their lung function was measured by pneumotachography (Jaeger Masterscreen System, Würzburg, Germany). If airways obstruction was confirmed, FEV_1 reversibility in response to 1·0 mg terbutaline was tested. If there was no response, the response to oral steroids (37·5 mg prednisolone once daily for 10–12 days) was tested. If the patient's FEV_1 was not reversible and he or she still wished to participate, randomised treatment assignment was obtained. Visit 1 took place at least 6 weeks after completion of the steroid reversibility test.

Patients were randomly allocated either inhaled budesonide or placebo. Budesonide was given as 800 μg in the morning and 400 μg in the evening for 6 months and 400 μg twice daily for 30 months. Budesonide was given in the Turbuhaler as budesonide powder for inhalation (400 μg per dose, 200 doses; Astra Pharmaceutical Production AB, Lund, Sweden). Placebo was also given in the Turbuhaler as lactose powder for inhalation (200 μg per dose, 200 doses; Astra Pharmaceutical Production AB). All study inhalers (budesonide and placebo) had the same appearance. Randomisation was masked and the randomisation sequence generated by computer at Astra. Study numbers were allocated in a consecutive order. The randomisation code was held by Astra and was not available to the researchers until the study had been completed.

Continuous use of inhaled corticosteroids other than study medication was not allowed. Oral, inhaled, or parenteral steroids could be used during exacerbations for up to three periods of 4 weeks each year. An exacerbation leading to use of additional corticosteroids was noted as an adverse event. Treatment with β_2-agonists of all kinds, theophylline, disodium chromoglycate, and mucolytics was allowed but kept constant. Concomitant use of β-blockers was not allowed during the study.

Participants were seen every 3 months. At each visit, measurements of spirometric indices (FEV_1, vital capacity, and forced vital capacity) were made 15 min after inhalation of 1·0 mg terbutaline. Values from the best of three spirometry tracings meeting the criteria of the American Thoracic Society were recorded, and the highest value of each variable was selected for analyses. At every other visit (every 6 months) additional measurements of FEV_1, vital capacity, and forced vital capacity were made before inhalation of terbutaline (ie, a reversibility test). At baseline, after 6 months, and at the end of the study (visits 1, 3, and 13), lung function was assessed three times on separate days during a 10-day period; the mean value was used in all analyses. For each individual, lung function was tested before or after 1200 h at each visit to limit variation due to (normal) diurnal variations. All readings were at normal body temperature and ambient pressure. In case of exacerbations or upper-airway infection in the preceding period, spirometry was repeated 4 weeks later. When comparing readings with predicted values for FEV_1, we used two sets of reference values, European reference values,[12] and values derived from healthy never-smokers in the CCHS.[11]

At every alternate visit, respiratory symptoms were recorded by use of a short questionnaire based on the UK Medical Research Council questionnaire. The following respiratory symptoms were registered: wheeze, wheeze without a cold, breathlessness at rest and at different grades of exertion, cough night and day, phlegm night and day, chronic phlegm, and chest tightness. An exacerbation was defined as an affirmative answer to the question, "Have you since your last visit experienced more cough and phlegm than usual?". Futhermore, detailed questions on smoking habits and changes in smoking habits were asked and carbon monoxide in expired air was measured.

The study was done in accordance with the principles stated in the Declaration of Helsinki. The study protocol, including the final version of the patients' information and informed consent form, was approved by the ethics committee of Copenhagen and Frederiksberg Communicipalities. All patients gave written informed consent before inclusion in the study.

Statistical analysis

Initially, a linear-regression analysis with rate of FEV_1 decline as the dependent variable was chosen, and on the basis of this statistical model we calculated that we would need 162 patients to detect a true difference in rate of FEV_1 decline of 20 mL per year with a power of 80% and a significance level of 5%. Because lung-function measurements within an individual are strongly intercorrelated, these data were analysed by a linear model for repeated measurements.[13]

The model for FEV_1 can be written as follows:

$$Y_{ij} = \gamma_j FEV_1\_0_i + \delta_{sex\,i} + \eta_{age\,i} + \alpha_{TX\,i} + \beta_{TX\,i} t_j + e_{ij}$$

where i is the individual, j is the number of the measurement, and the measurement itself is Y_{ij}. Age is that at entry, and t_j is the time for measurements j, where t_1 is set at 1, being the first measurement after start of treatment. The e_{ij} values are normally distributed with zero mean so that measurements from different patients are independent and the covariance between measurements from the same individual is unspecified but the same for all individuals. This covariance structure is also known as "unstructured" within patients. Data were analysed with restricted maximum likelihood in PROC MIXED of SAS (version 6.12).

This model assumes measurements within patients to be correlated, possibly with different correlations between measurement at different times. The model was verified against a larger linear model taking the effects of treatment, age, sex, smoking status, and their interactions into account. Specifically, none of the variables age, sex, or smoking had a significant effect on the rate of decline in FEV_1. We thus derived a model describing a linear rate of decline in FEV_1 with correction for age and sex. We analysed differences between treatment groups in changes in symptoms over time using weighted least squares for categorical repeated measurements.[14]

Results

290 individuals were included as a result of the initial screening; all individuals were assigned treatment as shown in figure 1. 87 patients withdrew from the study, 36 from the budesonide group and 51 from the placebo group. 16 patients in the budesonide group and 17 patients in the placebo group were withdrawn because of adverse events with no particular difference in pattern. Ten patients were withdrawn because of rapid deterioration of disease. 14 patients had been wrongly included, and 30 patients dropped out for various reasons not related to disease.

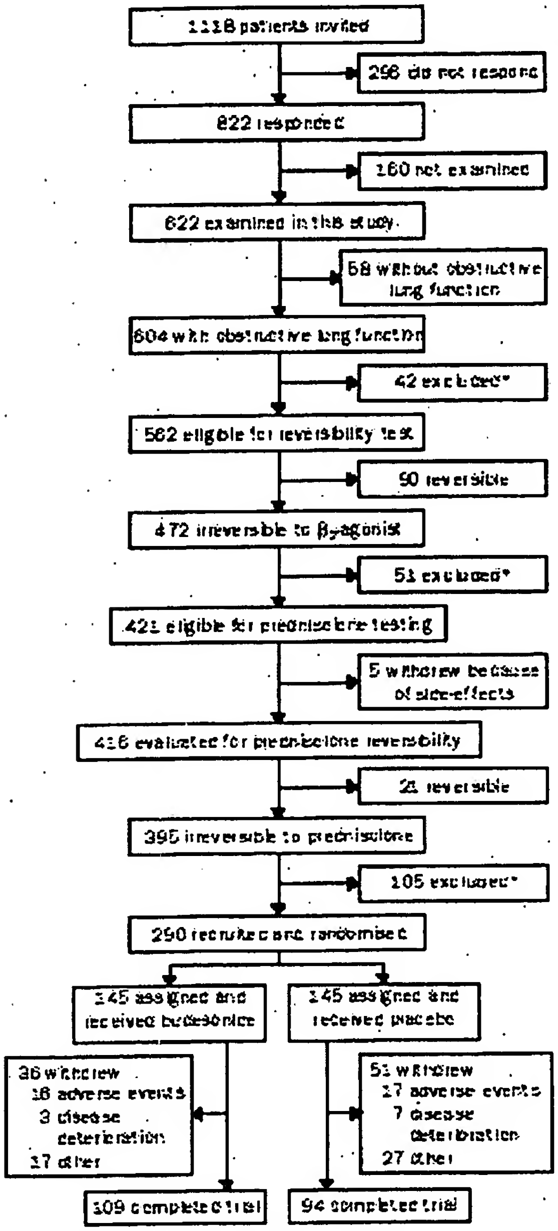

Figure 1: Trial profile

*Patients excluded because they did not want to participate further in the recruitment process.

Of the 203 patients completing the study, 198 made up the per-protocol population after exclusion of patients with compliance less than 75%, those who had exceeded the allowed amount of concomitant steroid treatment for exacerbations, and those who had received β-blockers during the study. Characteristics and treatment effects did not differ between the intention-to-treat population and the per-protocol population; only intention-to-treat results are shown. Baseline characteristics for the study population are shown in the table; 40% stated that they had no breathing problems. Figure 2 shows the distribution of participants in categories of COPD according to the European Respiratory Society according to European reference values and reference values from the CCHS.

	Budesonide (n=145)	Placebo (n=145)
Age (years)	59·0 (8·3)	59·1 (9·7)
Sex		
Male	85 (58·6%)	90 (62·1%)
Female	60 (41·4%)	55 (37·9%)
Spirometry		
Postbronchodilator FEV_1 (L)	2·36 (0·79)	2·39 (0·86)
Postbronchodilator FEV_1 (% predicted)*	86·2 (20·6)	86·9 (21·1)
β_2-agonist reversibility (% of baseline FEV_1)	8·1 (8·9)	7·2 (9·4)
Prednisolone reversibility (% of baseline FEV_1)	2·2 (8·7)	2·5 (8·9)
Smoking status		
Current	110 (75·9%)	112 (77·2%)
Never	5 (3·4%)	7 (4·8%)
CO in exhaled air (ppm)	14·2 (10·1)	13·3 (10·2)
Symptoms and signs†		
Chronic mucus hypersecretion	53 (37·1%)	48 (33·3%)
Wheeze with dyspnoea	35 (24·5%)	30 (18·9%)

Values are means (SD) when otherwise indicated.
*Using European reference values. †Assessed in 143 budesonide-group patients and 144 placebo-group patients.

Characteristics of treatment groups

No significant effect of budesonide was found on the rate of FEV_1 decline, the main outcome measure. We measured the change in FEV_1 from baseline by examining the linear slopes for each treatment group. The crude rate of loss of lung function was 41·8 mL per year in the placebo group and 45·1 mL per year in the budesonide group (figure 3). The corresponding estimated rates of FEV_1 decline were 49·6 mL per year and 46·0 mL per year. The difference in estimated rates of decline (3·1 mL per year [95% CI −12·8 to 19·0]) was not significant (p=0·70). The prestudy minimum relevant difference of 20 mL per year was outside the two-sided 95% CI. We found no effect of substratification on difference in rate of FEV_1 decline when dividing the population according to sex, smoking status, or baseline FEV_1 (cut-off 70% predicted), but the study was not powered for such subanalysis.

In both treatment groups, symptoms decreased substantially during the study period but no differences between the two groups were observed. The decrease in symptoms over time was most apparent for questions on breathlessness and least obvious in questions on cough and

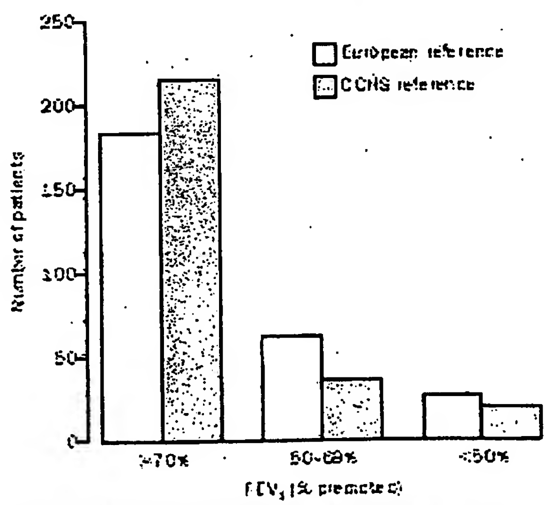

Figure 2: Distribution of patients in three categories of COPD according to choice of reference population

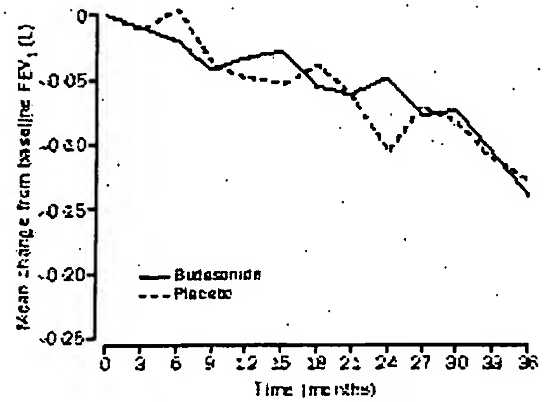

Figure 3: **Crude mean change from baseline FEV_1**
Post-bronchodilator values are shown.

chronic mucus hypersecretion. In the intention-to-treat population the number of patients with chronic mucus hypersecretion decreased from 53 of 143 to 18 of 91 in the budesonide group and from 48 of 144 to 14 of 77 in the placebo group. There were 155 exacerbations in the budesonide group and 161 in the placebo group, the difference was not significant. Reversibility to a β_2-agonist was not significantly affected by budesonide treatment, although a non-significant trend towards less reversibility over time was seen; in the placebo group, reversibility at visit 1 was 7·2% versus 8·2% of baseline FEV_1 at the end, whereas it decreased from 8·1% to 6·7% of baseline FEV_1 in the budesonide group.

Nine patients died during the study period, four in the budesonide group and five in the placebo group. None of the deaths were caused by COPD and all were unrelated to treatment. 55 other serious adverse events were recorded in 44 patients, 14 events in ten patients in the budesonide group and 41 events in 34 patients in the placebo group (p=0·001). None of the serious adverse events were believed to be related to treatment or treatment failure; one patient in the budesonide group was admitted to hospital twice because of exacerbations and one patient in the placebo group was admitted once.

11 patients in the budesonide group and eight patients in the placebo group had adverse events leading to withdrawal from the study. In total, 36 patients in the budesonide group and 34 patients in the placebo group reported temporary worsening of their disease during the study. Pneumonia was recorded in 16 patients in the budesonide and in 24 patients in the placebo group; 34 patients in each group had a least one reported viral infection. No specific pattern in non-severe adverse events was seen.

Discussion

This long-term single-centre study did not show an effect of budesonide on rate of decline in lung function in patients with irreversible COPD sampled from a large population survey. The small difference in rate of FEV_1 decline of 3·1 mL per year was not statistically or clinically significant.

Much controversy exists in the area of inhaled steroids in COPD, mainly because there have been no long-term controlled trials in patients with irreversible airflow obstruction and no features of asthma. Preliminary results from the large European multicentre study Euroscop,[15] comparing budesonide 400 µg twice daily and placebo for 3 years, caused debate about how to analyse and interpret the findings; the final results will show whether any effect of budesonide is present. The British multicentre study ISOLDE,[16] which compared fluticasone 500 µg twice daily and placebo, differs from ours and Euroscop because more severely ill patients were included. The study by Paggiaro and colleagues[9] also differed from ours because the mean baseline FEV_1 of their patients was about 0·5 L lower. They found significantly less severe exacerbations in the group treated with inhaled corticosteroids but no significant reduction in the total number of exacerbations. We recorded similar numbers of exacerbations in the budesonide and placebo groups but because we had only a crude measure of exacerbations, our study may not be able to detect subtle difference in grading.

Lack of statistical power does not seem to be the reason for the absence of an effect of inhaled steroids on decline in lung function in patients with COPD in our study, because the predefined minimum relevant difference was outside the 95% CI. Also, a lack of effect cannot be ascribed to underdosing; we chose a fairly high dose and the results did not change when the small number of patients with mean compliance less than 75% were excluded from the intention-to-treat population.

The rate of decline in FEV_1 seen in both study groups was smaller than the expected 50–60 mL per year. We cannot explain this discrepancy. However, our study differs from other studies in the way patients were recruited. All participants were recruited from a continuing epidemiological study on the basis of their FEV_1/vital capacity ratio.[17] Previous analyses from CCHS have shown rates of decline in FEV_1 of 25–30 mL per year among non-smokers and of 45–65 mL per year in heavy smokers with chronic mucus hypersecretion.[11,18] Several of our participants had very few symptoms, but whether this exclusion of referral bias plays a part is unknown. Steroid irreversibility was an important inclusion criterion in this study and for this purpose a 10-day course of 37·5 mg prednisolone was administered to all potential participants. This steroid irreversibility criterion might have led to selection of patients less likely to respond to inhaled corticosteroids. However, we are unable to look further into this possibility. Paggiaro and colleagues[9] reported an initial significant effect of inhaled corticosteroids on FEV_1. Any short-term effect could be explained by an effect on acute inflammatory changes, which is also seen in a proportion of patients when systemic steroids are given.[19] The likelihood of an acute response increases when features of asthma such as eosinophilia, bronchodilator response, and atopy are present. A long-term effect would, however, have to modify the natural course of the disease; reversal or even inhibition of such irreversible features as remodelling of the small airways, loss of alveolar attachments, and proteolytic destruction of elastic pulmonary tissue by inhaled corticosteroids does not seem likely. In contrast to preliminary reports from Euroscop, we found no isolated effect in women. Bronchial hyper-responsiveness seems to be more prevalent in non-asthmatic women than in non-asthmatic men;[20,21] therefore, inhaled steroids might be expected to have a differential effect in men and women.

Inhaled corticosteroids have a profoundly beneficial effect in asthma[22] and their central role in treatment cannot be disputed.[23] Thus, on the basis of our findings, the clinical efficacy of inhaled corticosteroids differs in asthma

and COPD. Studies of cell types and mediators from bronchoalveolar lavage fluid have also shown clear differences between asthma and COPD,[24,25] and a short-term study has shown that inhaled steroids have little effect, if any, on inflammatory processes in COPD.[26] Differentiation between asthma and COPD is therefore even more important in the daily clinical setting, and we should emphasise that cessation of smoking is still the only intervention with proven long-term efficacy of FEV_1 decline in COPD.[27] In addition, this differential effect of a potent anti-inflammatory drug questions the "Dutch hypothesis", which states that airway hyper-responsiveness and atopy are markers of a basic disturbance or constitution predisposing to the development of COPD.[28,29] This hypothesis may simplify the picture of obstructive airway disease by counting asthma and COPD together. However, the hypothesis has gained much support from longitudinal studies that show a significant effect of airway hyper-responsiveness on subsequent FEV_1 decline and symptoms.[30,31] In asthma, inhaled corticosteroids have a well-known effect on bronchial hyper-responsiveness and an almost implicit feature of the Dutch hypothesis is that inhaled drugs with anti-inflammatory properties should have an effect on the natural course of COPD. Our study is, however, limited in that we have no data on airway hyper-responsiveness for more detailed analysis of this issue.

Our study did not find an effect of long-term treatment with inhaled corticosteroids on decline in lung function in patients with mild to moderate irreversible airflow obstruction identified from screening a large random population sample. Comparison of these results with findings from other long-term clinical trials, soon to be published elsewhere, will enable us to assess whether inhaled corticosteroids have a part to play in COPD.

Contributors

J Vestbo was involved in the planning of the study and wrote the study protocol; T Sørensen assisted in examination of the participants; P Lange was involved in the planning of the study; A Brix developed the statistical model for lung function data; P Torre was responsible for all other statistical analyses; K Viskum was involved in the planning of the study, and was the physician responsible. All investigators were involved in preparing the paper.

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(x) Related Proceedings Appendix

None.